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THE RELATION BETWEEN HEART AND JOINT DISEASE INCLUDING "RHEUMATOID HEART DISEASE" AND CHRONIC POST-RHEUMATIC ARTHRITIS (TYPE JACCOUD)

BY

E. G. L. BYWATERS

From The Department of Medicine, Postgraduate Medical School of London and the Special Unit for Juvenile Rheumatism at the Canadian Red Cross Memorial Hospital, Taplow

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This study sets out to re-examine the relationship between rheumatic fever and rheumatoid arthritis in the light of a series of cases, studied mainly at the Postgraduate Medical School, on which biopsy or autopsy material is available. It will be concluded that there is every justification for regarding these two as separate diseases.

Historical Survey

Knowledge of the relationship between the disease of the heart and of the joints dates from comparatively recent times.

In 1788 David Pitcairn, in his lectures to the students of St. Bartholomew's, drew attention to the frequent occurrence of heart disease in patients who had been affected with rheumatism. The only record that exists of Pitcairn's original observations is in the second edition (1797) of the *Morbid Anatomy* written by his friend Matthew Baillie, to whom he passed his practice and the gold-headed cane (Macmichael, 1932). Edward Jenner, independently, in 1789 at a meeting of a Gloucestershire Medical Society at the Fleece Inn, Rodborough, reported *An affection of the heart following acute rheumatism*, but again this failed to reach print (Keil, 1936). Matthew Baillie himself fully endorsed Pitcairn's opinions, and William Wells, one of Baillie's closest associates, in his classic article on *Rheumatism of the Heart* (1812) gives the full story and a number of very pertinent cases illustrating this first association of heart and joint disease.

It was left to Jean Bouillaud in 1836 to emphasize this association in his famous law of coincidence: "in the great majority of cases of acute generalized febrile articular rheumatism, there exists a variable degree of rheumatism of the fibrous tissue of the heart. This coincidence is the rule and the non-coincidence the exception."

Between Wells in 1812 and Bouillaud in 1836, Laennec had introduced the stethoscope (1816), and thus it was, through the development of such new techniques, that the succeeding generation of French clinicians were able to establish so firmly the major clinical syndromes. It was not until 20 years later, with the accumulation of a good deal more clinical experience with these new methods, that this "law" was called into question.

In 1869 F. S. Jaccoud gave a clinical demonstration in the Hôpital de la Charité in Paris. The patient was a man of 29 who had had six attacks of articular rheumatism, the first four being severe but short-lived and the last two persistent. The first two attacks subsided completely, leaving neither symptom nor sign. In the third attack the patient developed a severe endocarditis which left him with dyspnœa, œdema of the legs, and well-marked valvular disease. Several months later a fourth attack of rheumatism occurred lasting 4–5 weeks, and once again the joints cleared up completely.

The heart lesion, however, persisted with the characteristic murmurs of aortic stenosis and insufficiency. Up to now the rheumatism had been of the classical Bouillaud type affecting only the large joints and clearing up rapidly. The fifth attack, however, lasted five months altogether: there was only slight fever this time compared with the severe fever of the previous attacks, and the pyrexia lasted for 2–3 weeks only. The joint pains, however, were severe, affecting the large joints for a very short time and now involving chiefly the hands and feet. After an interval of a few weeks the sixth attack of rheumatism occurred, affecting now the elbows as well, and lasting also five months.

Deformity of the hands developed for the first time in the third month of the fifth attack and was initially correctable, only later becoming permanent. At the demonstration, 7–8 months after the end of the sixth attack, the patient's hands showed muscle atrophy with marked deformity consisting mainly of severe ulnar deviation with slight flexion at the metacarpo-phalangeal (*MCP*) joints and extensions of the proximal and distal interphalangeal joints of the middle three fingers. The toes were also affected. There were no bony changes clinically and no crepitus: Jaccoud explained the deformity as subluxation due to the contracture of the fibrous cords which he demonstrated in the palm. The thumb, he said, was not affected, because the thickened aponeurosis is not attached thereto, nor was the contracture due to muscle change. The case was a rather unusual one but fitted into the category of *chronic rheumatism following acute rheumatic fever*. The more usual case in this category developed joint changes during convalescence: later the small joints stay painful and ultimately reach the stage of deformity with loss of power.

Homelle, in his article on rheumatism in Jaccoud's dictionary (1882) notes that following a series of attacks of frank rheumatism there persists some trace of inflammation in one or many joints but never to the same degree as with sub-acute and secondary rheumatism. " It is exceptional to see severe forms of arthritis succeeding."

Charcot, in his *Clinical lectures on senile and chronic diseases* at the Salpétrière, expressed himself thus (New Sydenham Society's translation by Tuke, 1881). " These complications " (endocarditis and pericarditis) " are not exclusively peculiar to this form of the disease. In the first place they are met with pretty frequently in subacute rheumatism in spite of the celebrated law of Professor Bouillaud, a rigorous and tyrannical law, if I may so express myself. . . . I have collected a considerable number of cases in which endocarditis has developed in chronic rheumatism without the disease ever having assumed an acute form." Pericarditis occurred 4 times in 9 autopsies on chronic rheumatism. He quoted two cases with characteristic deformities in which, however, the exact status of the endocarditis remains open to doubt.

Numerous examples of endocarditis in cases of chronic rheumatism were recorded towards the end of the century but it is difficult by modern standards to evaluate them.

Sir Alfred Garrod, in his *Treatise on Gout and Rheumatic Gout* (1876), records that he had " never met with an instance in which I could trace the occurrence of pericarditis or endocarditis to rheumatoid arthritic disease, however acute the joint affection may have been and I am of the opinion that this absence of cardiac inflammation is one of the best tests for distinguishing this malady from genuine rheumatism." He was aware of Charcot's conclusions but felt " inclined to pause a little as it is possible that the form of the disease in which acute cardiac inflammation has occurred may be rather that of true articular rheumatism of a very subacute character."

His son, A. E. Garrod of St. Bartholomew's, in his *Treatise on Rheumatism* (1890) records a case of a woman aged 34 who had suffered three attacks of rheumatic fever at 11, 18, and 24 years of age and three fairly severe articular attacks since the age of 24. Since the last of these she had noticed enlargement of the finger joints typical of rheumatoid arthritis with ulnar deviation. She also showed involvement of other joints and heart disease with a loud apical systolic murmur. A figure shows this post-rheumatic rheumatoid-like arthritis in the hands and a reduceable ulnar deviation without bony change, pain, or crepitus (Fig. 1).

Barjon summarized the possibilities well in 1897. (*a*) Acute and chronic rheumatism were essentially different diseases. (*b*) They were two diseases of the same family. (*c*) Simple coincidence accounted for the occurrence of heart and joint lesions in the same subject. In his series

of 62 cases, 6 showed mitral valvular disease, 4 aortic, and 3 pericarditis. The cardiopathy was verified in 3 of these, out of a total of 7 necropsies for the series. Two at least of his cases deserve quotation as they closely resemble the case described by Jaccoud.

Case III. Had had rheumatic fever æt. 12 and again æt. 14—the latter attack followed by endocarditis, ulnar deviation and deformity. A third attack occurred æt. 18. At 23 years of age he had been free of attacks for 3 years and was at work: he showed mitral stenosis and regurgitation with deformities of the hand (ulnar deviation, limitation, and flexion of the wrist).

Case IV. Had had rheumatic fever at 14, 18, and 26. Æt. 34 he developed swelling and flexion of the *MCP* joints and fixation of wrists joints with marked mitral regurgitation, still present 8 years later.

Most other references given by the older authorities are of little value, as none of them contain sufficient detail to exclude an acute rheumatoid arthritis with a systolic murmur or a rheumatic fever in older patients with degenerative joint disease, e.g. Spender (1889) talking of " osteo-arthritis as an immediate sequel of rheumatic pyrexia " confines himself solely and perhaps wisely to this remark—" It is of such sufferers that we constantly ask ourselves, especially in our Mineral Water Hospital, ' Is this case going off rheumatoidally? '."

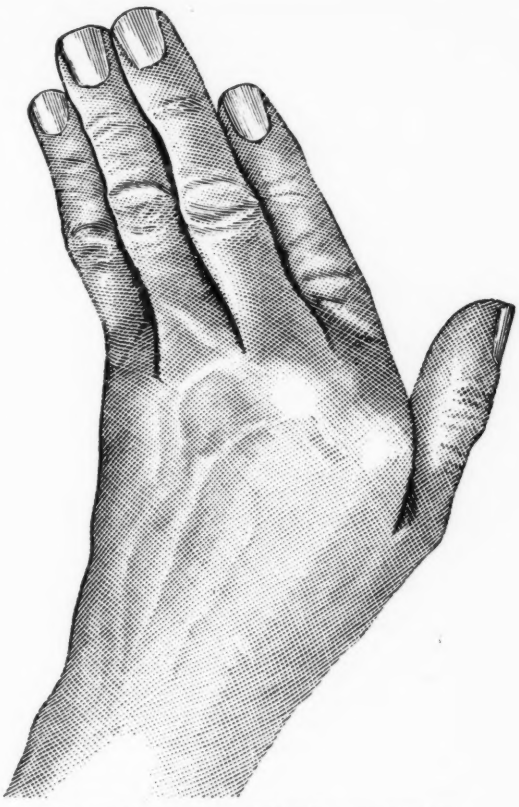

FIG. 1.—Post-rheumatic deformity reproduced from A. E. Garrod, 1890. See text.

It was not really until well on in the twentieth century, following the discovery by Röntgen in 1896 of X-radiation, that adequate diagnostic criteria began to be developed. Since the beginning of the century, very few English-speaking authorities have subscribed to the opinion that rheumatic fever may develop into a chronic articular type of rheumatism. Symes (1905) described and showed photographs of a girl of 16 whose deformities developed out of a previous attack of rheumatic fever at the age of 8, following which she had pains in the palms and fingers of both hands for many months with the gradual development of flexion deformities. Now there was neither pain, swelling, nor wasting: deformity was present consisting of flexion in the *MCP* joints and extension of the proximal interphalangeal (*PIP*) joints which straightened out with very little difficulty (Fig. 2). She had signs of mitral regurgitation and made a complete recovery with hot air baths. Although Bach (1935) stated that the " articula manifestations of rheumatic fever invariably subside completely and leave no sign of chronic joint involvement," he cited two cases with evidence of chronic joint involvement, seen by him among 400 cases of adult rheumatic heart disease attending the National Heart Hospital. Both had mitral stenosis with correctable ulnar deviation and periarticular swellings of the *MCP* joints without limitation. Fig. 3 shows an enlargement of one of his original X-ray prints, which he has kindly allowed me to see and reproduce. Besides ulnar deviation it shows healed erosions of the third and fifth metacarpal heads together with a slight degree of subluxation, following two attacks of rheumatic fever (see legend). The original legend reads " Rheu-

matic capsulitis with a rheumatoid type deformity." To-day most English-speaking modern text-books make no mention of this type of case.

On the Continent, however, the original conceptions of Jaccoud and Charcot have taken strong root. Grzimek (1932) found 43 per cent of 91 necropsy cases with " genuine arthritis deformans " showed heart valve lesions, whereas 429 control necropsies in the same period showed 18 per cent only. Klinge (1933) recorded 10 autopsies of chronic rheumatoid-like arthritis with or without nodule formation, of whom 8 showed the changes of rheumatic heart disease according to his criteria. While one would hesitate to criticise these cases in retrospect, it appears at least possible that Case 29 had rheumatic synovitis, judged by the illustrations. Case 36 had pericardial adhesions only, Case 38 had senile sclerosis of the aortic valve with probable osteo-arthritis. But even subtracting these, it leaves 5 of the 10 so affected. He thought that the differences between rheumatic fever and rheumatoid arthritis were quantitative rather than qualitative and that the diseases were fundamentally the same. Heart inflammation was correlated, he thought, with the intensity of the attacks, therefore slight in rheumatoid arthritis. He felt that in rheumatic fever the joints showed the same changes as in the early rheumatoid and that in rheumatoid, the viscera, e.g. the heart, showed the same late changes as in rheumatic fever.

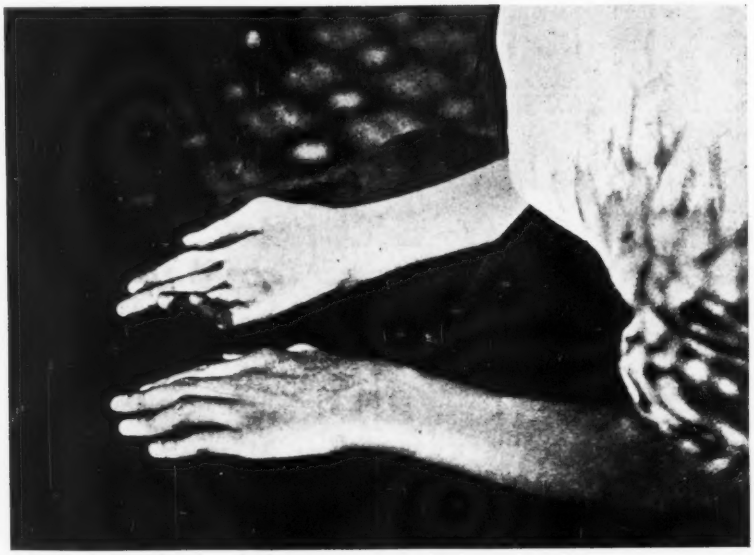

FIG. 2.—Photograph of hands in a case of post-rheumatic joint deformity recorded by Symes, 1905. (For clinical history, see text).

Many German-speaking authorities have accepted the implications of this classic work on the pathology of rheumatism (1933). Edstrom of Lund Sweden (1935), noted that a tendency towards chronic arthritis following acute rheumatic infection is more marked in patients who first have rheumatic fever at an advanced age. Out of 694 patients who had been attacked by acute rheumatic fever he found on follow-up that 10 were total invalids on account of chronic arthritis and 14 on account of chronic arthritis together with a heart lesion. Partial invalidism was found in 21 patients on account of chronic arthritis together with heart lesion. Elsewhere he stated that out of these 694 patients, there were 148 with chronic joint diseases of whom 74 also had heart disease. He showed that the number of patients showing the syndrome of chronic arthritis increased by every

FIG. 3.—Rheumatic capsulitis with rheumatoid-type deformity, reproduced from Bach, 1935. (See text.)

clinical attack of rheumatic fever, so that while only 4 per cent showed chronic arthritis at follow-up after one attack of rheumatic fever, among those who had been affected at least four times, more than 50 per cent showed chronic arthritis.

Freund (1929) in two years with 524 out-patients with joint disease observed 46 with secondary polyarthritis in the above sense; about 40 per cent showed cardiac defects. Fischer in 1933 records 201 cases of whom 65 had valvular defects. Pribram (1902) found clinical evidence of valvular disease in 19 out of 222 cases with chronic rheumatic polyarthritis and heart murmurs in 87.

Unfortunately, however, with the shift of emphasis associated with the rise of German pathology, clinical observation suffered. When English and American technological developments in clinical physiology and biochemistry in their turn took the lead, clinical descriptions became even less adequate, and there are few reports of this type of case in the twentieth century that even with all their adjuvant data will stand the test of time as well as Jaccoud's has done.

While many in the English-speaking world have suspected some relationship between rheumatic fever and rheumatoid arthritis (and a few thought this relationship a very close one, e.g. Dawson, 1935), it was not until 1941 when Bagenstoss and Rosenberg published their remarkably high figures of chronic rheumatic heart disease in autopsies of rheumatoid arthritis (53% compared with 5% in their control series) that general interest in this was re-awakened. Bayles from Boston found 6 cases (26%) with gross rheumatic valvular disease in a series of 23 autopsies on rheumatoid arthritis cases; 2 of the remaining 18 had adherent pericardium. Even if we exclude the 5 cases of ankylosing

spondylitis (of whom 2 had rheumatic heart disease) the incidence does not become appreciably lower (22%). However, Bayles thought that this high incidence (compared with his clinical incidence of 5%) was due to selection, since 4 out of the 6 were known to have rheumatic heart disease during life.

From Minneapolis, Fingerman and Andrus (1943), found 19 out of 61 autopsy cases of rheumatoid arthritis showed rheumatic heart disease (31%). Bennett (1943) found that in 48 autopsied rheumatoid arthritic cases only 7 had rheumatic heart disease for certain (15%) and 3 rather doubtfully (6%) (3 more had pericarditis and 3 died of myocarditis of unknown ætiology). Clark and Bauer surveying what is most probably the same group found pericarditis in 44 per cent, some degree of valvulitis in 20 per cent, and in two cases lesions in the heart similar to rheumatoid subcutaneous nodules, and a peculiar aortitis and aortic valvulitis in one case: in only one case, however, could a certain diagnosis of rheumatic heart disease be made. Smythe (1943) found 5 out of 10 rheumatoid necropsies showed both gross and microscopical lesions of rheumatic heart disease. The highest incidence recorded is that of Young and Schwedel (1944) from New York; of 38 cases, 24 showed valvular disease and 9 pericarditis. They include in their series of 38 rheumatoid autopsies, however, 25 with spinal involvement and only 13 without: the exact status of these is difficult to determine since only 2 are stated to have Marie Strumpell spines and of the 23 remaining with spinal involvement, 14 (i.e. 60%) are female and in no case was the spine affected without involvement of limb joints as well. These two facts are contrary to the findings in any other series of spondylitis and although involvement of the spine is known to occur in rheumatoid arthritis proper, particularly during childhood, it is exceedingly rare. The authors also specifically excluded hypertrophic arthritis of the spine. Thus if we exclude cases with spinal involvement, 10 out of 13 cases showed heart disease (77%) although in 3 of them the pericardium was the only structure involved.

TABLE I

AUTOPSY INCIDENCE OF RHEUMATIC HEART DISEASE IN RHEUMATOID ARTHRITIS

Series		Total	No. with V.D.H.	Percentage	No. with pericarditis
Charcot	1881	9	0	0	4
Kast	1901	17	5	29	2
Pribram	1902	13	3	15	2
Grzimek	1932	91	47	42	—
Klinge	1933	10	7	70	—
Mayo Clinic	1944	30	14	47	3
R.B.B.	1943	23	6	26	2
Harvard	1943	48	7–10	15–21	—
Minneapolis	1943	61	19	31	—
Michigan	1943	10	5	50	—
Montefiore	1944	38	24	63	9
B.P.G.M.S.	1949	31	7	23	2
Total since	1941	241	82	34	16

Although the criteria for the diagnosis of rheumatic heart disease vary slightly from series to series, figures summarized in Table I have depended for the most part upon gross deformities of the valves; evaluation of microscopic stigmata leads on to much more difficult conclusions, e.g. Hall and Anderson (1943) conclude that while only 66 per cent of 100 consecutive autopsied hearts show thickening of the mitral valve, a total of 95 per cent showed stigmata of rheumatic heart disease if microscopical criteria were included. Similarly, according to Barahona and Gorena (1947), of 200 controls, abnormal endocardial vessels were seen in 21 per cent, Aschoff bodies in 7 per cent and rheumatic stigmata without abnormal vessels in 19 per cent, i.e. a total of 40 per cent of normals show signs of rheumatic fever in the past (Table II).

TABLE II

INCIDENCE OF RHEUMATIC HEART DISEASE IN CONTROL AUTOPSY MATERIAL

Series		No.	Gross R.H.D. (%)	Micro. (%)
B.P.G.M.S.	1949	1000	6·4	—
Mayo Clinic	1941	All	5	—
Grzimek	1932	429	18	—
Barahona and Gorena	1947	200	—	40
Hultgren	1948	100	—	11
Hall and Anderson ..	1943	124	10	90

Koletsky and Karsner conclude from their study of calcific aortic stenosis that all such cases are ultimately rheumatic in origin. It had previously been believed that a high proportion of them were purely degenerative in origin, and Hultgren (1948) concluded that only 11 out of 100 consecutive autopsies blocked by the Gross method, aged 16–86, had rheumatic heart disease, although 46 out of 100 had calcium deposits in the aortic valve. Our own series will be discussed in the light of these findings in the next section.

Finally, a new type of heart disease was recorded in 1941 by Bagenstoss and Rosenberg when they described two cases (in full in 1943) with rheumatoid granulomata in the heart muscle. They were not convinced that this bore no relation to rheumatic fever. These findings have been confirmed in one case published by Raven, Weber, and Price (1948) and in one published by Gruenwald (1948). Thus there seems to be historically three main conclusions:

(1) That rheumatic fever and rheumatoid arthritis are separate diseases (this does not exclude their occasional occurrence in the same person).

(2) That rheumatic fever and rheumatoid arthritis are closely allied, if not the same disease.

(3) That certain types of rheumatic fever may go on to produce a chronic type of rheumatism distinguishable, albeit with difficulty, from rheumatoid arthritis and that certain types of rheumatoid arthritis can produce heart lesions and valvular deformities and pericarditis distinguishable, albeit also with difficulty, from the lesions of rheumatic fever. The conclusions that we shall draw from the data presented in this paper favour the last viewpoint.

THE INCIDENCE OF HEART DISEASE IN AUTOPSIED CASES OF RHEUMATOID-LIKE ARTHRITIS

Between 1935 and 1948, in a series of approximately 4500 autopsies performed in the Department of Pathology (Director—Professor J. H. Dible) at the Postgraduate Medical School, London, 22 cases had what was interpreted by experienced clinicians as rheumatoid arthritis (4 of these 22 occurred prior to 1939 and were not seen personally: 3 of the 4 showed valvular lesions—see later case histories). There were included, in addition, 2 patients with rheumatoid arthritis who died and had autopsies at other hospitals, and 3 with Still's disease, thus making a total of 27 cases; 4 cases of spondylitis ankylopoietica in men came to autopsy during the same period.

In the series of 27 post-mortem cases of rheumatoid-like arthritis, excluding spondylitis ankylopoietica but including Still's disease, no significant heart lesion was found in 14, coronary thrombosis with infarction in 2, and a terminal verrucous endocarditis without any lesion of the underlying valve in one case (Table III). Two cases showed merely slight calcification in the aortic ring at the cusps; both were over 70 years and in the absence of other gross evidence of a rheumatic process, this was considered a degenerative lesion (see later discussion).*

Thus of 27 cases, 19 showed no cardiac lesion relevant to the present study (70%) (Table III *a*). Of the remaining 8 (Table III *b*), 3 showed lesions of the heart that we have interpreted as rheumatoid, and 5 showed rheumatic heart disease (18%). We suggest later, however, that 1 and possibly 3 of the 5 cases had not rheumatoid arthritis at all, but the chronic post-rheumatic type described

* Unfortunately in these 2 cases and in 3 others out of the 27, no sections of the heart were available for review.

TABLE III

CASES OF RHEUMATOID ARTHRITIS AND SPONDYLITIS WITH NECROPSY

Case No. and initials	Sex	Age at death	Duration joint disease (yr.)	Description joints	Heart failure (F)	Heart wt.	Pericardial lesions	Myocardial lesions	Valve lesions	Cause of death
				(a) Rheumatoid arthritis without significant heart disease						
1 G.L.	M	53	7/13	Early knee involvement (biopsied).	—	— (2)	—	—	—	Pyelonephritis. (Prostatic enlargement.)
2 F.A.	F	59	2	Typical R.A. with nodules (2).	F	+ (2)	—	—	—	Hypertensive heart disease and encephalopathy.
3 G.C.	M	67	6	Severe R.A. Nodules+.	—	360 g.	—	—	—	Broncho-pneumonia.
4 W.G.	M	72	6	Fibrous ankylosis knee, hip, etc. Typical deformity of hands.	—	310 g.	—	—	—	Broncho-pneumonia and bronchiectasis.
5 M.A.	F	52	7	Typical rheumatoid arthritis.	—	270 g.	—	—	—	Pyelonephritis.
6 A.S.	F	57	10	Typical R.A. with bone erosion.	—	—	—	—	—	Carcinoma breast.
7 D.M.	F	53	15	Typical R.A. with bone erosions and deformities.	—	(2) —	—	—	—	Empyema and broncho-pneumonia due to perf. ca. œsoph.
8 F.S.	F	71	18	Typical R.A. Bone erosions and deformities. (Sjogren's synd.)	F	490 g.	Pericarditis.	Infarcts old and recent.	—	Coronary thrombosis.
9 H.M.	F	67	20	Typical R.A. *MCP* joints with ulnar deviation.	—	280 g.	—	—	—	Carcinoma stomach.
10 O.S.	F	45	20	Active severe R.A. with bone erosion.	—	140 g.	—	—	—	Synovioma with metastases.
11 N.R.	F	49	20	Typical R.A. with ankylosis.	—	300 g.	—	Petechiæ	—	Nephritis. Hypertension.
12 H.W.	F	53	21	Healed R.A. lesions with bone erosions.	—	320 g.	—	—	—	Paralytic ileus after op. carc. of ovary.
13 F.B.	M	74	22	R.A. hands, wrists, with ankylosis.	F	(2) —	Adherent	Infarct	—	Coronary thrombosis.
14 A.W.	F	66	22	Typical R.A. Bone erosions, nodules, Felty's syndrome.	F	+	—	—	Valves healthy. Some thickening of mitral curtain.	Multiple pulmonary infarcts.

TABLE III—*continued*

TABLE III—*continued*

CASES OF RHEUMATOID ARTHRITIS AND SPONDYLITIS WITH NECROPSY—*continued*

Case No. and initials	Sex	Age at death	Duration joint disease (yr.)	Description joints	Heart failure (F)	Heart wt.	Pericardial lesions	Myocardial lesions	Valve lesions	Cause of death
Rheumatoid arthritis without significant heart disease—continued										
15 S.C.	F	75	29	Old R.A. deformities. Nodules.	—	310 g.	—	—	Terminal verrucous mitral and aortic: no inflamm. lesion.	Uræmia due nephritis. Cachexia.
16 S.J.	F	12	2	Typical R.A.	—	—	—	—	—	Hepatitis.
17 V.H.	F	13	2	Typical R.A.	—	162 g.	—	—	—	Hepatitis.
18 A.W.	F	74	12	Typical R.A. with bone erosions.	—	260 g. (2)	—	—	Healthy except slight calc. aortic ring.	Bronchitis.
19 E.G.	F	72	10	Typical widespread R.A. with bony change.	—	300 g. (2)	—	—	Calcified aortic valve only.	Carcinoma stomach. Broncho-pneumonia.
(b) Rheumatoid arthritis with heart disease										
20 M.I.	F	72	++	Typical R.A. gross deformity. Nodules.	No R.F. Failure 1/52. Fibrill. S.M. and D.M.	450 g.	Pericard-itis.	—	Rheumatoid granulomata in aortic ring and deformity of valve.	Heart failure.
21 J.G.	M	29/12	14/12	Typical Still's disease.		—	Oblit.	Myocard-itis, non-specific.		Broncho-pneumonia.
22 S.T.	M	67	1	Early R.A.	—	350 g.	Adherent	—	Slight calcification in aortic cusp.	Peritonitis due to perf. appendix.
23 K.N.	F	69	20	Typical R.A. ankylosis.	—	360 g.	—	—	Mitral fibrosis. Terminal endocarditis.	Broncho-pneumonia.
24 M.W.	F	57	15	Most jts. fixed by contractures and ankylosis (1).	Heart failure with fibrillation.	240 g.	Oblit.	—	Mitral stenosis. Other valves healthy but partly calcified.	Pneumonia.
25 M.G.	F	45	4	Arthritis dating from R.F. attack. *MCP* swelling and ulnar deviation (2).	R.F. æt. 41. Mitral systolic. Heart failure.	—	Pericard-itis.	Many large Aschoff nodes.	Mitral stenosis: recent vegetations.	Heart failure.
26 A.T.	F	70	44	Occ. pain and disability in jts. for many years. Externally R.A. of hands (1), (2).	R.F. æt. 7, 17, 47. Fibrillation. Mitral S.M. and D.M.	+	—	Fibrosis	Mitral and aortic stenosis: tricuspid valves thickened.	Carcinoma.
27 A.W.	F	72	4	Gross ulnar deviation dinner-fork deformity and fibrous ankylosis of fingers. No nodules: no other jts.	Fibrillation. Mitral stenosis.	390 g.	Oblit.	Healed Aschoff nodes.	Mitral stenosis and terminal verrucous endocarditis. Other valves healthy.	Amyloidosis. Uræmia.

TABLE III—*continued*

CASES OF RHEUMATOID ARTHRITIS AND SPONDYLITIS WITH NECROPSY—*continued*

Case No. and initials	Sex	Age at death	Duration joint disease (yr.)	Description joints	Heart failure (F)	Heart wt.	Pericardial lesions	Myocardial lesions	Valve lesions	Cause of death
					Spondylitis ankylopoietica					
28 J.K.	M	57	++	Spond. ank.	——	(2)	——	——	——	Fat embolism. (Traumatic fractured spine.)
29 S.L.	M	48	32	Spond. ank. Gross chest deformity.	F. and auric. fibrill. R.V. prepond. Mitral S.M.	430 g.	——	——	Mitral fibrosis. (No stenosis or incomp.)	Heart failure. Cor pulmonale.
30 W.A.	M	62	37	Spond. ank. peripheral jt. involvement (2).	——	(2)	——	——	Calcified aortic valve only.	Carcinoma stomach. Broncho-pneumonia. (Psoriasis.)
31 A.O.	M	57	30	Psoriatic arthritis with ank. spond.	——	280 g.	——	——	——	Carcinoma (? primary lung). Amyloidosis.

(1) = X-rays not seen.
(2) = Sections not seen.

originally by Jaccoud. If this were true it would bring the incidence of rheumatic heart disease complicating rheumatoid arthritis proper *by our criteria* to 7 per cent and for the age group 41–90, to 8 per cent (2/24), a figure that is comparable to the incidence in the control post-mortem material in these decades (including our own—6%). It is realized that, with these small numbers, it would be incorrect to conclude that rheumatic heart disease was either more or less common in rheumatoid arthritis than in the general population: this figure differs, however, from those published in other post-mortem series (see Table II) and accords much better with clinical data (Table IV).

TABLE IV

CLINICAL INCIDENCE OF RHEUMATIC HEART DISEASE IN RHEUMATOID ARTHRITIS

Series	Year	Total No.	Percentage with R.H.D.
Ballantyne	1898	293	18
McCrae	1915	500	5
Boas and Ripkin	1924	26	11
Coates	1931	—	4
Wetherby	1932	350	2
Dawson and Tyson	1933	100	7
Kahlmeter	1934	85	15*
Monroe	1936	267	4
Colver	1937	69	1
Hench and Rosenberg	1941	All	0
Bayles and McGinn	1943	100	5
Ellman	1944	100	8
Lucchesi *et al.*	1947	50	0
Rogen	1947	22	4
Rosenberg, *et al.*	1949	150	3

* 8 per cent of 48 if chronic primary polyarthritis only is considered.

CLINICAL AND PATHOLOGICAL CORRELATIONS

We shall therefore examine in detail the clinical and pathological findings in these 8 cases with combined heart and joint disease and hope to establish, if not quantitatively, at least qualitatively that three groups emerge:

(*a*) Rheumatoid arthritis with rheumatoid heart lesions

(*b*) Rheumatic fever with rheumatic heart disease, followed at a later date by rheumatoid arthritis.

(*c*) Rheumatic fever with rheumatic heart disease complicated by chronic (post-rheumatic) fibrous rheumatism of the Jaccoud type.

Additional cases will be cited from the literature and from our own practice in some of whom biopsy material has been obtained.

(*a*) *Rheumatoid arthritis with rheumatoid heart lesions*

Case 20. M.I., f., age 69 at her first admission. She was deaf and dumb and had been an invalid from arthritis for many years. Examination showed wasting with inelastic skin, and scanty hair. Jugular venous pressure, (J.V.P.) normal. Soft goitre, neck movements limited. Nails ridged and the movements of fingers limited (some muscular wasting). Wrists fixed in flexion. Elbows: bilateral ulnar bursal swellings. Pulse: occasional dropped beat. Blood pressure (B.P.) 150/85 mm. Hg. Apex beat 3½ inches from midline. Occasional extrasystole. No murmurs. Œdema of feet and ankles and healed varicose ulcers of the tibiæ. Right hip and knee fixed in flexion. Toe and ankle movements nil. Hæmoglobin 9·4 g. per cent. No albuminuria. Apyrexial. Discharged on ferrous sulphate after one month.

She was re-admitted three years later and died within a few hours. For the past three years she had been in bed and unable to help herself. One week before admission she started vomiting; this was followed by sweating and cough. She was breathless; systolic and diastolic murmurs were heard at the apex by the admitting officer. J.V.P. to angle of jaw. Apex beat in 6th space: fibrillation. B.P. 140/100. (130/65 in hospital.) Heart sounds were thought to be normal later. Goitre, deformities, wasting present as before.

Swelling of the knees, feet, and hands. Elbows now limited to 30° flexion. X-ray of hands: changes typical of rheumatoid arthritis.

Diagnosis. Congestive heart failure with auricular fibrillation and rheumatoid arthritis.

Necropsy.—Marked rheumatoid deformity, collapse of left lung, recent adhesive pericarditis with fibrin exudate. Heart enlarged (450 g.). Right and left ventricles hypertrophied and dilated. Mitral valve normal. Aortic valve cusps grossly thickened and opaque with some fusion of commissures; coronary arteries large and normal. Liver: nutmeg pattern. Kidneys 240 g. and 160 g. with some ischæmic scarring. Spleen firm. Thyroid—goitre.

Microscopically, the joints showed typical rheumatoid changes (Fig. 4). The heart showed rheumatoid granulomata in the aortic ring, partly calcified (Fig. 5 and 6). Olecranal tissue showed subcutaneous nodule formation.

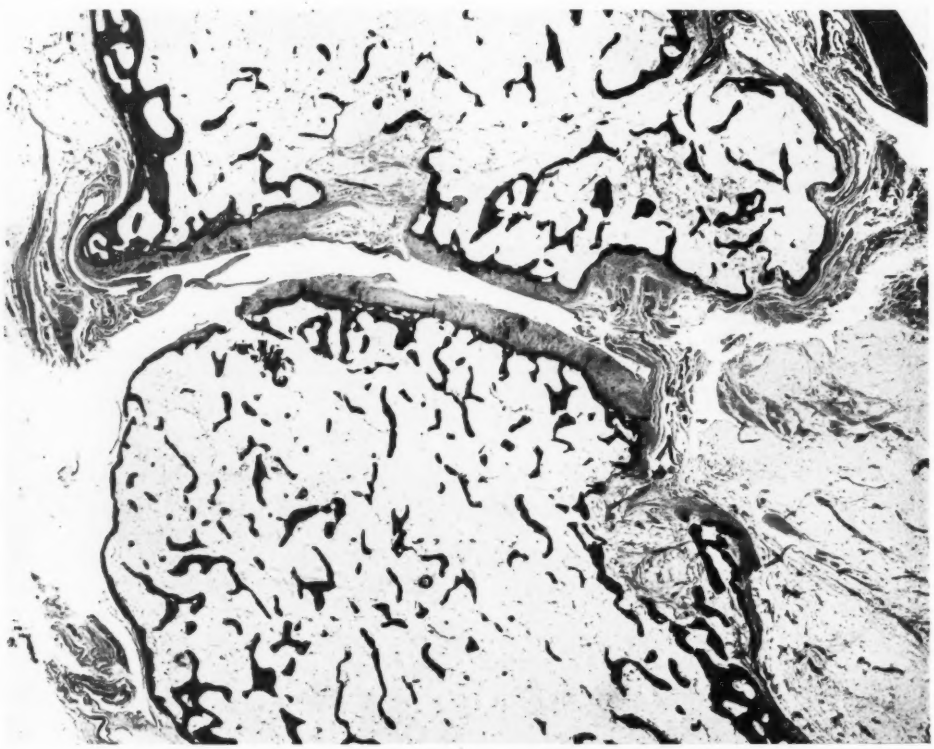

FIG. 4.—Microphotograph (×9) of *MCP* joint (right index) showing diminished joint space, pannus creeping over margins of cartilage, destruction of cartilage at margins and a central defect extending into the bone marrow and bordered by regenerated fibro-cartilage. Case 20.

This is the only case in the series with valvular deformity due to rheumatoid granulomata. She died of congestive failure which had lasted some time judged by the nutmeg liver and had occurred despite her relative immobility. There was no microscopic evidence of healed rheumatic myocarditis, the coronary vessels appeared normal, the goitre did not seem to be toxic, and there was no clinical evidence of hypertension. No Wassermann reaction was performed but there was no specific aortitis. Thus most of the usual causes of failure were absent and we attribute the failure to fibrillation and rheumatoid heart disease. It will be noticed that some considerable fibrosis is apparent in the micro-photograph in the neighbourhood of the granulomatous lesion.

FIG. 5.—Low-power view (× 19) of aortic ring and base of cusp showing multiple rheumatoid granulomata extending up into the base of the aorta and into the valve as well as throughout the ring area, in places calcified. Note also marked fibrosis of myocardium. Case 20.

Accompanying the aortic valve lesion was a fibrinous pericarditis. Fig. 7 shows how closely it resembles the chronic rheumatoid process in the synovial membrane of the same patient: we believe that this is a specific rheumatoid pericarditis.

Cases similar to this were described first by Bagenstoss and Rosenberg (1941 and 1944). They concluded that the lesions in their two cases could be brought under the classification of rheumatic heart disease and doubted whether they represented a separate disease entity, largely because in one case Aschoff-like structures were present in the myocardium and in the second perivascular scars that have been interpreted as healed Aschoff bodies were present.

The third case was described by Raven, Weber, and Price in 1948, death being due to a cardiac condition characterized pathologically by large rheumatoid granulomata scattered through the heart muscle. Interstitial fibrosis was present but no Aschoff nodes were seen. Mitral stenosis and dilatation of the left auricle was present. There was a history of " rheumatic fever " at the age of 20 and rheumatoid arthritis started 11 years later, progressing to gross deformity and a massive and almost universally distributed crop of rheumatoid nodules. A fourth case has recently been published (Gruenwald, 1948) in a 57-year-old man with rheumatoid arthritis for 6 years. Autopsy showed rheumatoid arthritis of knee joints, destruction of carpal bones, etc., and granulomata characteristic of rheumatoid arthritis in the right atrium, tricuspid valve, pleuræ, and splenic capsule. Clark and Bauer (1948) mention two such cases.

A lesser degree of rheumatoid heart disease consists of pericarditis only. This complication occurs usually below the threshold of clinical consciousness: we have recorded a case elsewhere (Bywaters, 1949) where it was first picked up on a routine electrocardiogram and only later was

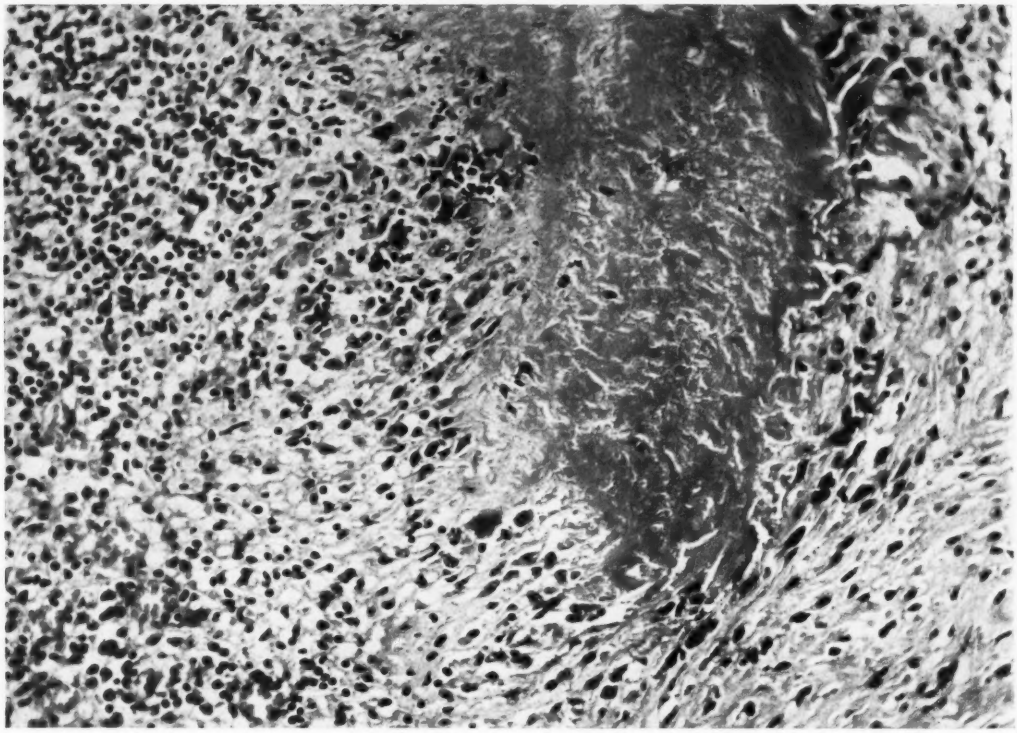

FIG. 6.—High-power view of rheumatoid nodule in aortic ring (×235) showing palisade formation, central necrosis and surrounding lymphocyte and plasma cell infiltration. Case 20.

friction heard. Symptoms were minimal. Usually pericarditis is only diagnosed post mortem where the visceral and parietal layers are seen to be adherent the one to the other, sometimes with a few inflammatory cellular collections—old fibrin and blood vessels left in the scar.

In children, however, pericarditis is not only more frequent (it was present in the 3 autopsies originally described by Still) but also more widely known to occur and therefore more frequently observed during life. In our Taplow series of 20 cases of Still's disease (or rheumatoid arthritis starting before the age of 16) pericarditis has been detected clinically thrice. In the autopsied series one of the three cases of Still's disease showed pericardial obliteration as well as pleurisy and perisplenitis, and will be detailed in full elsewhere. Briefly, the boy (Case 21) was $2\frac{1}{2}$ years old at death and had had arthritis for one year. Clinical evidence of pericarditis was sought but not found: the only other heart lesion was a widespread focal interstitial (non-rheumatic) myocarditis.

In the 24 adult cases of this series with chronic rheumatoid-like arthritis on whom necropsies were performed, adherent pericardium was noted seven times, in 2 cases associated with myocardial infarct and in 3 with rheumatic heart disease, leaving only 2 in whom it could possibly be attributed solely to the rheumatoid process. In the case already detailed with aortic valve deformity due to rheumatoid heart disease, the pericarditis closely resembled the granulomatous lesion in the synovial membrane (Fig. 7). In the other the rheumatoid process was of about one year's duration:

Case 22. S.T., m., æt. 68 at death, had had recurrent painful swellings of left knee since a football accident æt. 37. When admitted to hospital, æt. 60, for dyspepsia no abnormality found.

Æt. 66, developed painful swelling of shoulders, fingers, wrists, knees, and ankles lasting one month. A year later, left knee swollen, and then pain in right hip, left ankle, shoulders, wrists, and hands which became swollen.

Examination showed painful limitation of movement, swelling of left 2nd and 3rd *MCP* joints with weakness and atrophic skin. Fluid in knee joint. Hæmoglobin 10·8 g. Blood sedimentation rate (B.S.R.) 65 and 85 mm./hr. Heart: no abnormality. No nodules. X-rays: left basal fibrosis and chronic arthritic changes in the right acromio-clavicular joint: no changes in hands.

Æt. 68, stiff neck for three months and stiffness and swelling of the hands. B.S.R. 18 mm./hr. Typical deformities of rheumatoid arthritis in the hands; treated by diathermy. Four weeks later, admitted with a perforated appendix, and died after 4 days. Heart sounds normal. B.P. 140/85.

Necropsy showed broncho-pneumonia and peritonitis due to perforated appendix. The heart showed old adhesive pericarditis: there was slight calcification in the aortic cusp and calcification of coronary vessels. All the valves appeared normal. Rheumatoid changes were seen in the 2nd and 3rd fingers and in the right shoulder grossly and histologically. X-rays showed bone erosions.

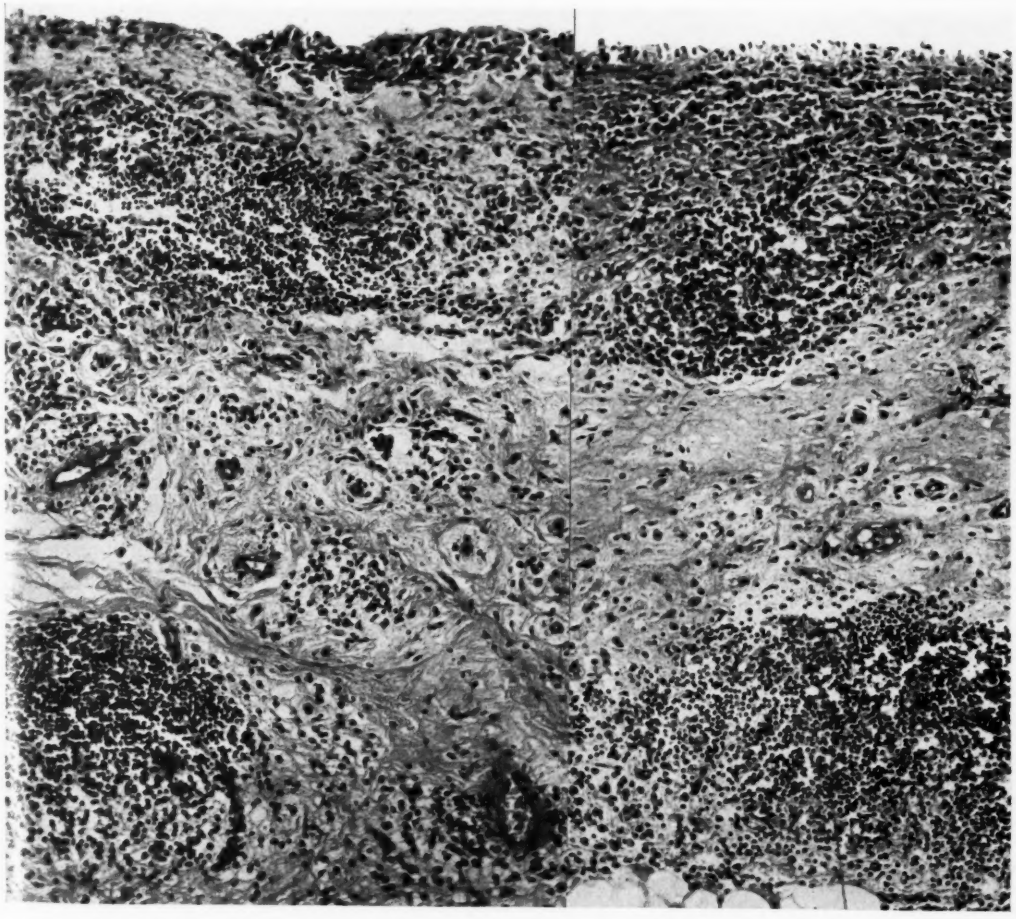

FIG. 7.—Microphotographs of synovial membrane of knee (left), pericardium (right). Both ×120. Note marked similarity, with hyperplasia and fibrin incorporation of lining membrane, diffuse plasma and lymphocyte infiltration deeper. Case 20.

(*b*) *Rheumatic fever complicated by rheumatic heart disease with later development of rheumatoid arthritis*

Case 23. K.N., f., æt. 69 at death, had had rheumatoid arthritis for 20 years, affecting her hands and legs and had been unable to walk for 10 years.

Examination. Systolic murmur at apex. Fusiform swelling of fingers. Knees and ankles fixed in flexion. Death was due to confluent broncho-pneumonia.

Necropsy. The heart (360 g.) showed terminal endocarditis on the mitral valves. Microscopically these were thickened and showed marked fibrosis and distortion, with increased vascularity. The joints showed typical active rheumatoid arthritis microscopically with destruction of cartilage and ankylosis.

Case 4. M.W., f., æt. 57; died within 24 hours of admission: lobar pneumonia of 4 days duration. Crippling rheumatoid arthritis since 42 years of age.

Examination. There were contractures of both upper and lower extremities. Hands and feet were markedly deformed with an old rheumatoid arthritis. No X-ray seen.

Necropsy. Most joints were fixed by contractures and ankylosis. Microscopically the synovial membrane was typical of rheumatoid arthritis. The pleural cavities were obliterated and there was apical scarring and lobar pneumonia. The pericardium was completely obliterated. The mitral valves were short, thick, fibrosed, and partially calcified, showing stenosis. Other valves were healthy. No myocardial lesions were seen microscopically. The spleen showed sugar-icing.

Although neither of these gives a history of rheumatic fever, the heart lesions were typical of rheumatic heart disease and the joint lesions of rheumatoid arthritis. Three other cases also had rheumatic heart disease, but because of atypical features in the joint disease they will be discussed in the next section as doubtful (Case 27), possible (Case 26), and probable examples (Case 25) of post-rheumatic joint disease rather than of rheumatoid arthritis.

If there were no special relationship between rheumatoid arthritis and rheumatic fever, rheumatic heart disease should occur in cases of rheumatoid arthritis in the same proportion as in the general population—affecting in this age group about 5–10 per cent according to gross findings at autopsy. If finer pathological criteria are adopted it is possible to assert that 90 per cent of people have had and bear scars of rheumatic heart disease, although only 10 per cent (12 out of 124) show valvular lesions in the commonly accepted sense of the term (Hall and Anderson, 1943).

It is perhaps surprising in view of the frequency of Group A hæmolytic streptococcal infections and the occurrence in 20 per cent of such infections of a post-streptococcic state that is indistinguishable from mild forms of rheumatic fever (Rantz, Boisvert, and Spink, 1947) that so small a proportion are affected clinically. Clinically, rheumatic heart disease occurs in a relatively small number of cases of rheumatoid arthritis (e.g. 2% Wetherby, 1932, 8% Ellman, 1944, 0% Lucchesi *et al.*, 1947, 5% Rogen, 1947, 7% Dawson, 1933, 0% Hench and Rosenberg, 1941, 5% Bayles and McGinn, 1943) (see Table IV). It should occur in an even smaller proportion if cases with a history of rheumatic fever are excluded (e.g. 5% Fischman and Gwynne, 1948). A much higher proportion of heart disease in rheumatoid arthritis (30%) is claimed by Feiring (1945), but it seems highly probable that the criteria adopted and the short period of observation—a few months only, have allowed of the inclusion of cases with subacute rheumatism and rheumatic fever.

In a well-documented case the temporal relationship between the two coincident diseases is quite clear.

W.H., f., æt. 31. Rheumatic fever, when aged 6 and 28. Sixteen months before entry, swelling, stiffness and pain in third right *PIP* joint; later *MCP* joints, knees, and ankles affected.

Examination. Mitral stenosis, aortic regurgitation, swelling of *MCP* and *PIP* joints with weakness and wasting (Fig. 8), involving also right wrist, left knee, left ankle, and left *MTP* joints. On radiography, osteoporosis, subchondral rarefaction and diminished joint space in wrist and finger joints. B.S.R. 103, falling to 90 mm./hr. 6 weeks later. Synovial fluid of rheumatoid type (low sugar, high protein). Follow-up when æt. 34 showed chronic arthritis wrists, ankles, and fingers and radiologically erosion of *PIP* joints. B.S.R. has remained between 23 and 38.

(*c*) *Rheumatic heart disease with chronic fibrous rheumatism* (*Type Jaccoud*).

During recovery from rheumatic fever cases are not infrequently seen which present during the subsidence of rheumatic activity a periarticular swelling of joints, best marked in the *MCP* joints,

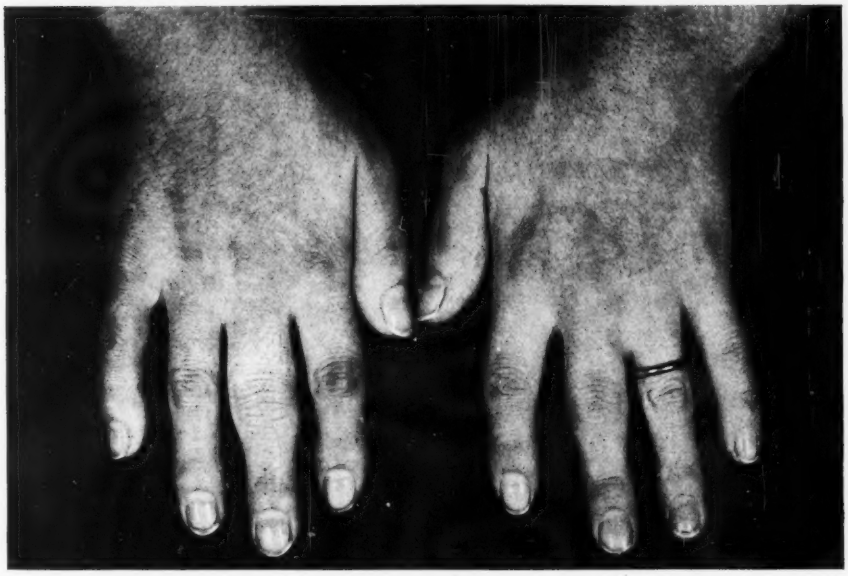

FIG. 8.—Hands showing spindling of interphalangeal joints. Case W.H.

sometimes in the *PIP* joints. This is usually associated with marked nodule formation, as in the following case.

E.G., f. First attack of rheumatic fever at the age of 15. Six months later she developed a second attack with arthritis, chorea, marginate rash, and pericarditis. The joints subsided rapidly on salicylates. As the B.S.R. came down from 85 on entry to 45, 11 days later, spindling appeared in the *PIP* joints due to prenodular thickening and nodules (biopsied). These lasted for a period of four months although the B.S.R. fell to normal (11 mm./hr.) after 35 days. The accompanying figure shows the simulation of rheumatoid arthritis (Fig. 9). At follow-up two years later, no residual swelling was seen.

In general these cases subside completely even when there have been changes even more marked than the preceding case. These severe types seem to be more common in (but not confined to) adults.

R.W., m., æt. 44, admitted with a rash and painful joints, gave a history of pain and swelling in his joints when 26, lasting 17 weeks. Tonsillitis occurred one month before present admission and painful stiffness in his joints nine days before.

Examination showed some effusion with redness of right knee and both feet; soft apical systolic murmur and widespread circinate but slightly raised (urticarial) rash. Sedimentation rate 116 mm./hr. P–R interval 0·22–0·24 seconds with electrocardiographic evidence of pericarditis and ventricular extrasystoles. Fever and arthritis responded to salicylates. Nodules (biopsied) developed on olecranon and knuckles and B.S.R. fell slowly to 33 by the 150th day. The hands were still rather closely stiff, the *MCP* joints and wrists slightly limited with periarticular thickening. There was also wasting of the interossei. X-rays showed marked rarefaction, estimated quantitatively by a previously described method (Bywaters, 1948) and shown in the accompanying charts (Fig. 10A and 10B). Seen one year and again four years from onset, patient had mitral stenosis, no joint involvement clinically or radiologically, and a B.S.R. of 5 mm./hr.

These cases probably represent the early stages (the " forme fruste ") of the Jaccoud syndrome; sometimes, however, more chronic changes occur as in the following case.

J.G., f., æt. 12, developing her first attack of polyarthritis and chorea two weeks before admission. Following salicylate therapy, joint systems subsided leaving her with diastolic murmurs at apex and base.

FIG. 9.—Hands showing spindling due to periarticular nodule-like plaques with later resorption. Case E.G.

After ten weeks, nodules and periarticular swelling developed, particularly *MCP* 2 and 3 left. She ran a prolonged active course lasting seven months with a B.S.R. initially 83 mm./hr. falling gradually to 40 by 20 weeks and 14 by 30 weeks from admission. At eleven months the *MCP* joints showed marked periarticular swelling with slight degree of fixed flexion and correctable ulnar deviation. There was some interosseous wasting (Fig. 11). X-rays showed no bony change. Two months later (i.e., when she had been relatively inactive, except for a recurrence of chorea for six months with an average weekly B.S.R. over this time of 13 mm./hr., a biopsy of the still swollen right index *MCP* joint showed normal synovial membrane and marked basophilia of interfibrillar ground substance of the capsule (Fig. 12).

Recently, however, a case was observed through the kindness of Dr. Coghill of the West Middlesex Hospital, London, of a degree thought to be previously unrecorded during life, which we think is of similar status to the cases with chronic arthritic changes of advanced type such as Klinge has examined post-mortem.

O.L., f., æt. 25 years. In 1940 at the age of 17, she developed a first attack of rheumatic fever with polyarthritis followed by chorea. Her left wrist and both knees were swollen and painful but not her finge

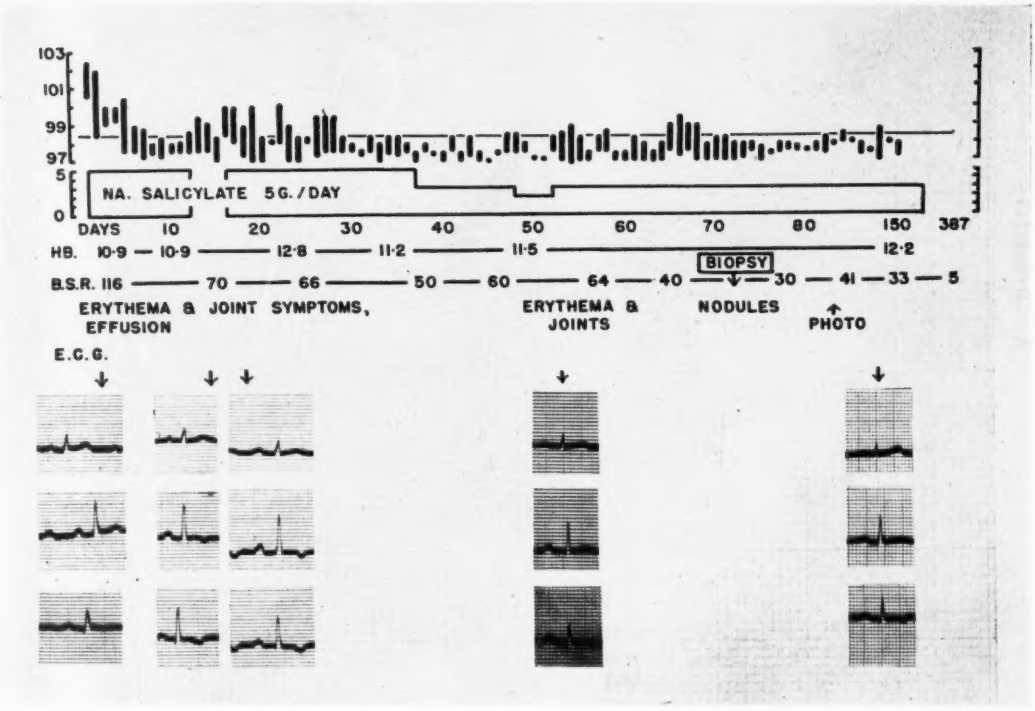
103
101
99
97
5
0
NA. SALICYLATE 5G./DAY
DAYS 10 20 30 40 50 60 70 80 150 387
HB. 10·9 — 10·9 — 12·8 — 11·2 — 11·5 — 12·2
BIOPSY
B.S.R. 116 — 70 — 66 — 50 — 60 — 64 — 40 — 30 — 41 — 33 — 5
ERYTHEMA & JOINT SYMPTOMS, EFFUSION
ERYTHEMA & JOINTS
NODULES
PHOTO
E.C.G.

FIG. 10 A.—Chart of case showing prolonged rheumatic fever joint involvement. Case R.W.

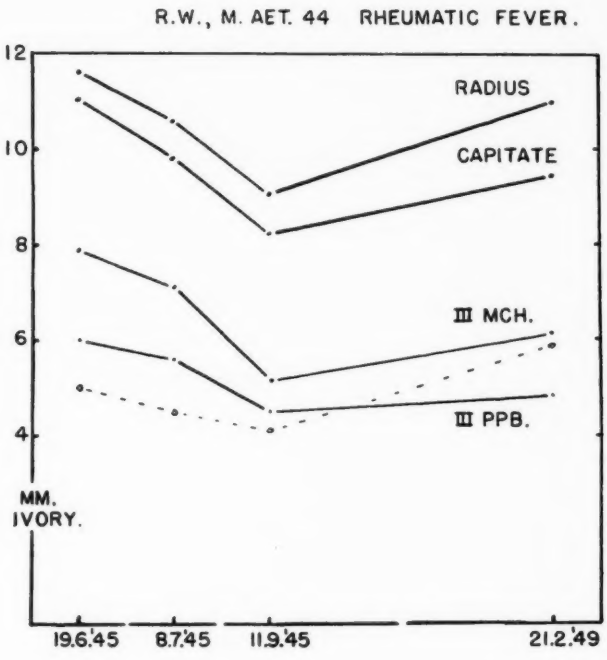

FIG. 10 B.—Osteoporosis developing rapidly in hands (same case) of prolonged rheumatic fever joint disability. During period of decalcification sedimentation rate was raised. Follow-up shows return to normal bone opacity. Case R.W.

FIG. 11.—Hands showing flexion deformity at *MCP* joints and slight ulnar deviation with periarticular swelling. Case J.G.

oints. She had nodules on her elbows. On discharge a month later, some aching of her fingers was noted for some months and she noticed that the knuckles were red and swollen. The chorea returned for a short time in 1941 but disappeared without medical treatment. In 1943 she noticed a disability in her hands; she was unable to hold the palms of the hands closely together (as in the attitude of praying) (Fig. 13), and the fingers particularly on the ulnar side began to move outwards. This ulnar deviation could be corrected voluntarily (Fig. 14). There has, however, been no pain in the joints or any rheumatism for the last five years and the patient has felt in good health. She has continued with her work as a medical secretary and typist and has no complaint of the joints. She was admitted because of recently noticed scotomata. Examination showed a block of the upper ciliary retinal artery with œdema of ciliary retina (Mr. P. H. N. Matthews). There was evidence of mitral stenosis and aortic incompetence (pre-systolic and loud systolic murmur at the apex and early diastolic basal murmur). Screening showed slight enlargement of the left auricle and the œsophagus displaced slightly backward in the first oblique position. B.P. 115/75. No pyrexia, no petechiæ, no nodules. Blood cultures negative. No urinary abnormality. Hæmoglobin 100 per cent (Haldane). W.B.C. 8400. Spleen not palpable. B.S.R. 4 mm./hr. The hands both showed ulnar deviation (Fig. 14) more on the right side than on the left, particularly involving the 4th and 5th phalanges, together with gross swelling of the *MCP* joints (2, 3, 5 right and 1, 2, 3, 5 left and 3 *PIP* right). There was no limitation of movement except incomplete extension, but some interosseous wasting and contracture of palmar fascia. Gross creaking and some crepitus was heard on extension against slight resistance of the flexor tendons of the 2nd and 5th right fingers. The ulnar deviation could be voluntarily corrected and thus maintained, but on relaxation the fingers assumed the deviated position.

X-rays showed ulnar deviation and bony erosion involving the *MCP* heads of the right 3 and 5 (doubtful right 4). There was some evidence of previous inflammatory change affecting the ulnar styloid of both sides and sharpening of the bones adjoining the radio-ulnar joint right (Fig. 15). Biopsy (Fig. 16) showed normal synovial membrane and basophil fibrosis with pyknotic remnants between the bundles of collagen in the capsular tissue.

It is thought that these changes were due to prolonged rheumatic activity and that bone erosions were due to rheumatic fever. It is not thought that they represent rheumatoid arthritis. Valuable evidence against this is given by the lack of symptoms, the biopsy, and the normal B.S.R.

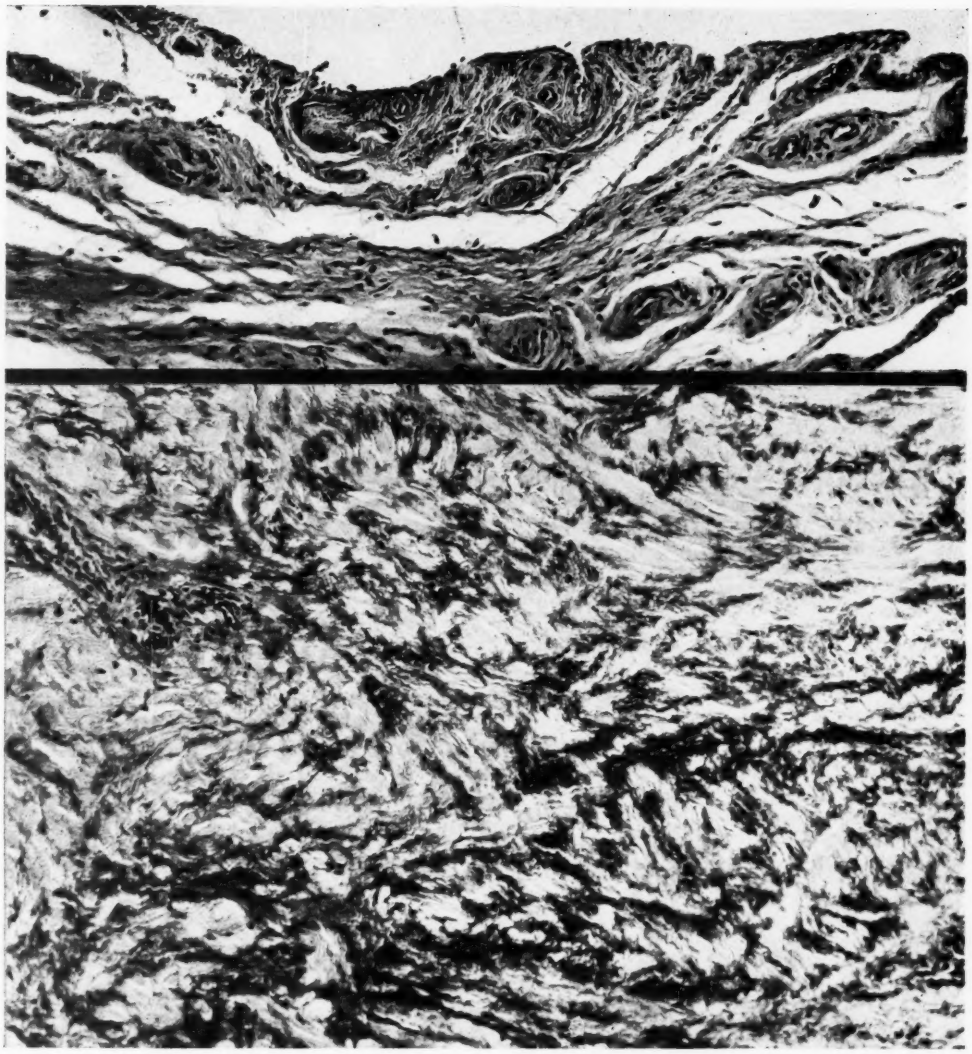

FIG. 12.—Microphotograph (× 130) of synovial membrane and capsule from 2nd *MCP* joint right, showing marked accumulation of basophil ground substance between collagen fibres and normal synovial membrane. Case J.G.

A further case showing what is thought to be a more advanced degree of this is seen in the autopsy series.

Case 25. M.G., f., æt. 45. Four years ago, tonsillitis, followed by pleurisy and rheumatic fever—pain in most joints and nodules on elbows and legs—in bed for six months. Five weeks before admission sore throat, pain in limbs worse, affecting hands, shoulders, and knees; some dyspnœa on effort and œdema of feet. On examination ulnar deviation and swelling *MCP* joints right hand. Tenderness and slight limitation of thumbs. Very slight limitation of shoulders by pain. Heart showed mitral systolic and later diastolic murmurs. X-ray shows subluxation and hook erosions of the *MCP* heads (Fig. 17). Fever (101·5°).

FIG. 13.—Hands showing palmar contracture. *MCP* flexion, and soft tissue swelling. Case O.L.

FIG. 14.—Hands showing ulnar deviation correctable voluntarily. Case O.L.

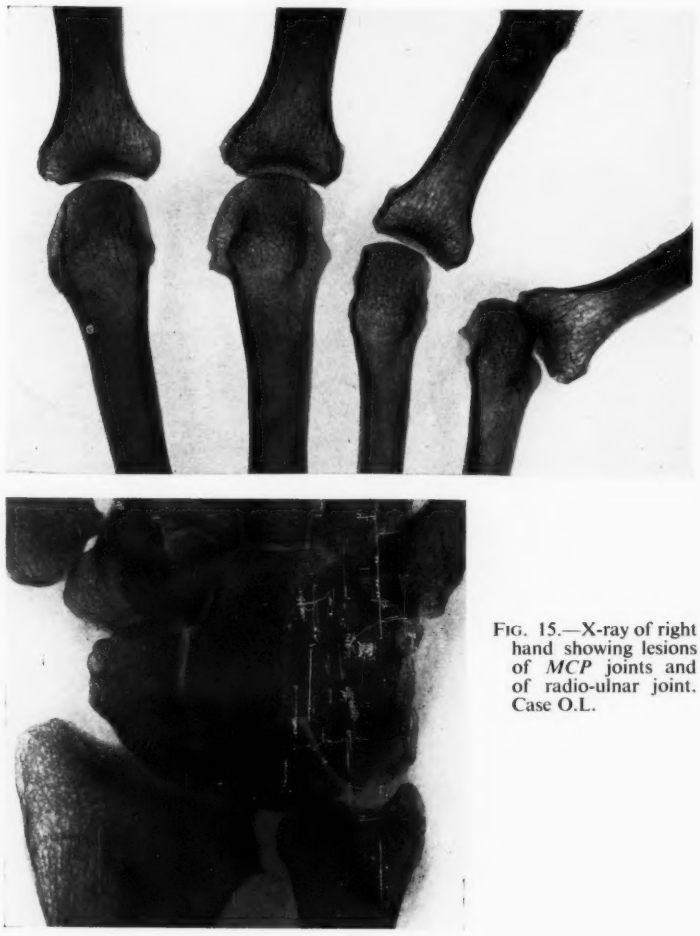

FIG. 15.—X-ray of right hand showing lesions of *MCP* joints and of radio-ulnar joint. Case O.L.

B.S.R. 112 mm./hr. Group A hæmolytic streptococci isolated from throat. She died of sudden heart failure one month after admission.

Necropsy showed pericarditis, chronic mitral stenosis, acute mitral and aortic endocarditis with many large Aschoff nodules. No joint sections taken.

These X-ray changes are very similar to those seen in the preceding case but represent a more advanced and a more burnt-out aspect.

Lastly, two other cases from the autopsy series are detailed.

Case 26. A.T., f., æt. 70. Rheumatic fever æt. 7, 17, and 47 years and rheumatoid arthritis "for years: occasional pain and disability in joints for many years." On examination systolic and diastolic murmurs were heard at apex; auricular fibrillation was also noted.

Necropsy. Externally rheumatoid arthritis of hands (no further examination of joints). The heart was enlarged and showed thickening of the tricuspid valves; mitral and aortic stenosis; and terminal verrucous endocarditis. The pericardium was healthy, the myocardium showed fibrosis but no recent activity. Carcinoma of cæcum.

FIG. 16.—Microphotograph (×175) showing normal synovial membrane and fibrosis of connective tissue between collagen bundles with some nuclear fragmentation. Case O.L.

As neither X-rays nor section of joints were available, it is impossible to decide on the exact status.

Case 27. A.W., f., was first admitted to Hammersmith Hospital in July 1935 complaining of tinnitus, vertigo, and palpitation. She was then 59 years of age, and gave a history of good health all her life, her only illness being scarlet fever 30 years previously, *with rheumatism*. The notes specify that she had not had rheumatic fever. Examination at the time showed the presence of a soft apical systolic murmur at the apex, the apex beat was thought to be 12 cm. from midline; B.P. 150/84. X-ray showed enlargement of left ventricle and unfolding of the aorta.

Second admission in March 1936, under Dr. Wood, for functional dyspepsia. Heart sounds normal with no adventitious sounds. Attended for one year.

She was next seen in June 1943 complaining of pain in muscles of left arm. Some tenderness was noted

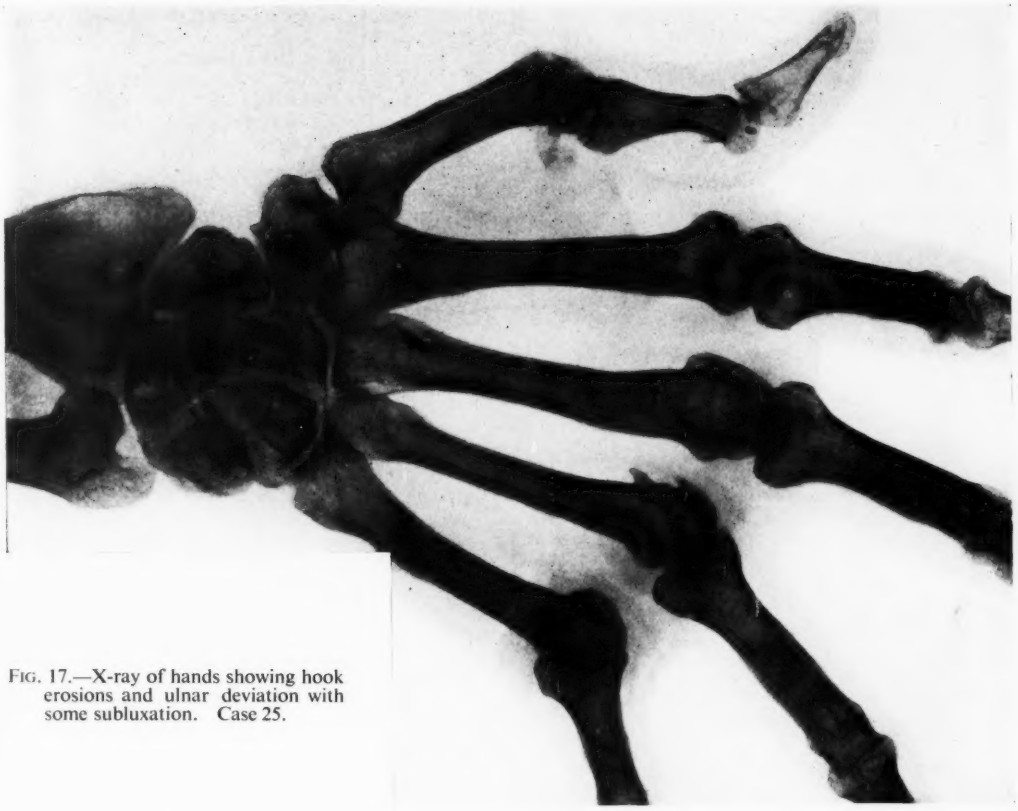

FIG. 17.—X-ray of hands showing hook erosions and ulnar deviation with some subluxation. Case 25.

there and in left buttock; a systolic murmur was heard in the heart. No ankle œdema. Temperature 99·4° F. A month later, pain in the shoulders and other joints shifting about, worse in the mornings. She was thought at that time to have rheumatoid arthritis or heart disease. Heart and lungs were recorded as normal. There was pain on movement of the joints but no limitation. B.S.R. 14 mm./hr. Westergren. She was treated with radiant heat and exercises, and from October 1943 was confined to bed for 7 weeks with a generalized acute rheumatoid arthritis. Temperature, 100° F. for a week or so.

In July 1944 she was readmitted (Professor McMichael) complaining of dyspnœa on exertion developing gradually over the past two years and swelling of the legs in the evening. For the previous six months she had had stiffness, pain and swelling of her hands and later of her ankles and knees. Physical examination revealed the presence of mitral stenosis: a blowing systolic and a rumbling diastolic murmur at the apex and a systolic at the base. B.P. 145/75. Her joints were thought to be characteristic of rheumatoid arthritis with ulnar deviation of both hands; right more than left. The *PIP* joints were swollen and the grip was weak. There was œdema and stiffness of ankles: slight swelling of knees but no fluid. She was afebrile at the time. B.S.R. 65 mm./hr. Hæmoglobin 11·6 g. R.B.C. 4,600,000. The joints were not X-rayed.

She was admitted for the fourth and last time in 1948. Up to two days before admission she had been able to walk about and managed a few stairs. She then developed palpitations and pain in the chest.

On examination there was auricular fibrillation and a systolic murmur in all areas. B.P. 150/70. Œdema of ankles and sacrum, enlargement of liver and albuminuria. There was gross ulnar deviation with dinner-fork deformity of the fingers and fibrous ankylosis of the fingers (E.G.L.B.). There were no nodules and no other joints actively involved. X-rays showed peculiar well-defined hook-erosions of the *MCP* heads, with a considerable amount of dislocation: wrist-joint changes with periostitis and erosions of the metatarsal heads (Fig. 18).

Investigations showed continued albuminuria, low plasma proteins (3·4–4·1 g./100 ml.) and a low œdema protein (750 mg.). Congo red showed 65 per cent elimination from the serum in 1 hour. B.S.R. 15 mm./hr. Her condition remained stationary until 4 days before death when congestive failure became worse.

Necropsy showed rheumatic heart disease with partial obliteration of pericardium by loose adhesions; dilation and hypertrophy of both auricles. Mitral valve admitting one finger only, with shortened chordæ, a thickened shelf-like band and many vegetations 0·5–1·0 mm. in diameter along the contact margin. Tricuspid aortic and pulmonary valves were normal. There was some coronary atheroma and calcification. Heart 390 g.

Sections show some perivascular fibrosis consistent with healed Aschoff's lesions but no sign of activity. The valve showed fibrosis and vascularity but no active valvulitis, the vegetations being terminal thrombotic ones. The knee joint showed fibrillation of the cartilage and some destruction of the internal meniscus. Our opinion on the gross specimen was that this was degenerative joint disease. Sections of synovial membrane therefrom showed a few lymphocyte collections, a few plasma cells and pigment-containing macrophages consistent with a relatively inactive and healed inflammatory lesion. There was no pannus formation. Sections of the right index *PIP* joint showed destruction of cartilage at several points with replacement by fibrous tissue together with a marked decrease in joint space due to encroachment by the synovial membrane up to the margin of cartilage (Fig. 19). Active inflammatory synovitis was absent although a few round cells and plasma cells were visible. There were in addition organizing and packed pulmonary emboli, from thrombosis of femoral and iliac veins, together with amyloid disease affecting especially the kidneys.

FIG. 18.—X-ray of hands and feet showing deformity with hyper-extension of proximal interphalangeal joints and flexion, with subluxation, of *MCP* joints. Note hook erosions. Case 27.

The joint lesions in this case represent either healed and inactive rheumatoid arthritis or a severe degree of chronic fibrous rheumatism, following rheumatic fever. In favour of the latter are the peculiar hook erosions (as in Case 15) and the deformity which is the same as Jaccoud originally described. These two cases are sufficient to make one examine very carefully any similar case coming along, since if we had been able to examine sections of clinically affected joints we should probably be able to speak with more certainty. Bennett (1943) mentions briefly a very similar case presenting a clinical picture that was difficult to distinguish from mild rheumatoid arthritis.

"She was a woman of 45 years of age who had been told that she had rheumatic fever and rheumatic heart disease five years before her last hospital admission. She then complained periodically of pain and stiffness

in most of her joints during the previous five years. On several occasions tenderness, swelling, and limitation of motion were elicited in the digital joints. Post-mortem, typical valvular, myocardial and pericardial lesions of rheumatic heart disease. Examination of the spine, knees, metatarsophalangeal and interphalangeal joints of the most severely affected toes and the metacarpophalangeal and interphalangeal joints of one affected finger revealed a mild diffuse lymphocytic, plasma cells and mononuclear leukocytic infiltration in the synovial and subsynovial tissues. All other articular structures were negative."

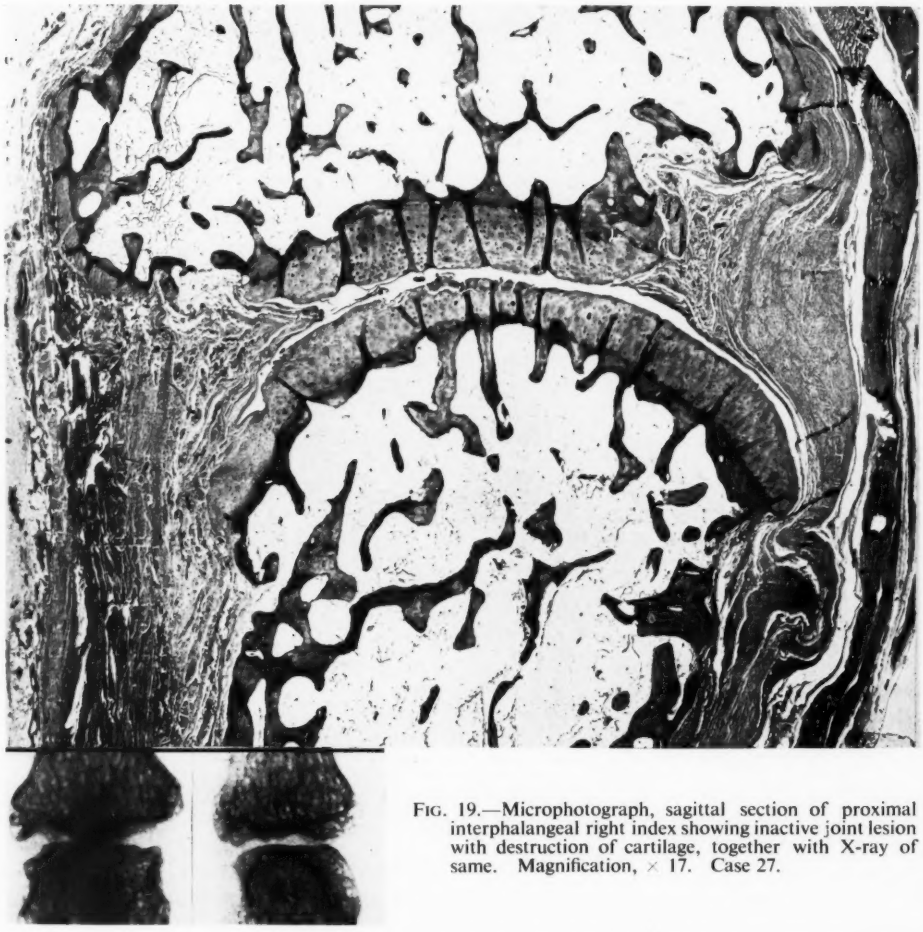

FIG. 19.—Microphotograph, sagittal section of proximal interphalangeal right index showing inactive joint lesion with destruction of cartilage, together with X-ray of same. Magnification, × 17. Case 27.

He concluded that, in the absence of ætiological evidence to the contrary, it would seem advisable to continue to look upon rheumatic fever and rheumatoid arthritis as separate and distinct entities.

A few cases have been described besides those previously cited by Garrod, Symes, and Bach, that may fit into this category. Careful and detailed clinical accounts in the classical French tradition have been published of a "rheumatisme dislocant" following rheumatic fever, first by Lereboullet and Moujon in 1920 and then by others (Table V). These four cases closely resemble each other: following several attacks of rheumatic fever, residual deformity develops consisting of ulnar deviation and subluxation at the *MCP* joints. This is passively correctable and the ligaments are lax.

Crepitus may be felt. It is most marked in the right hand and in the fourth and fifth fingers, but may affect the feet. There is no functional disability, and the B.S.R. may be normal or raised. X-ray may show no bony abnormality or there may be minor lesions of the carpal bones and of the metacarpal heads. It is said to be distinguished from Jaccoud's type by the presence of laxity rather than fibrous contraction, but it seems to the present author that " rhumatisme dislocant " and Jaccoud's fibrous rheumatism represent the same complication of rheumatic fever.

TABLE V

Author	Age and sex	Age at onset of R.F.	No. of attacks of R.F.	Age at onset of joint	Heart lesion
Lereboullet and Moujon ..	F. 26	13	4	20	Mitral lesion.
Boidin, Vallery-Radot and Roux	F. 51	8	3	31	Mitral lesion. Failure, fibrillation.
Boidin and Droguet	F. 72	13	3	30	Mitral lesion. Failure, fibrillation.
Arlet and Dunglas	F. 42	12	3	27	Mitral lesion.

Still, in his original paper "on a form of chronic joint disease in children" described an "extremely rare " form of which he had seen only one case, a boy, aged 5, whose fingers had become stiff from the formation of fibrous nodules over the tendons at the age of 3½ years. Limitation and swelling of the elbows and wrists followed. " There was no evident affection of the phalangeal joints although there was marked limitation of movement, the terminal phalanges being flexed and some of the proximal phalanges hyper-extended." There was a loud apical systolic bruit and subcutaneous fibrous nodules on finger, elbow, and hip. " In this particular case although there was no history of acute rheumatism, the association of a cardiac bruit with fibrous nodules was, I think, sufficient proof of the rheumatic nature of the joint affection. There can be no doubt that it is identical with the disease described by Jaccoud as chronic fibrous rheumatism." Many others have also invoked Jaccoud's name but with less authority for doing so. It is widely held that Brigidi and Banti have published a necropsy on such a case (1880); in fact there was no valvular disease of the heart at all in their patient.

A case more comparable to that of Jaccoud's was described by Worster-Drought (1930). A woman, aged 27, had suffered attacks of rheumatic fever at the ages of 12, 14, 17, 18, and 22, after which she developed severe ulnar deviation with periarticular swelling but no limitation. She had rheumatic heart disease. Young and MacMahon (1935) describe 2 patients in detail and list a further 8 with atrophic arthritis and mitral stenosis. Their first patient, after an attack of acute rheumatic fever, aged 15, developed two years later a deformity in the hands and feet. At the age of 18 her deformities were the same as they were seen to be on examination at the age of 37, suggesting that the lesions had healed within 3 years of the onset of acute rheumatic fever. The heart was in congestive failure with stenosis and fibrillation. The joints showed flexion with lack of complete extension in the *MCP* joints, ulnar deviation and osteoporosis. Other cases were not detailed so fully.

I had seen up to 1948 one such patient, a woman under the care of Dr. Bauer at the Massachusetts General Hospital, Boston, in 1937, in whom there was little radiological change or joint symptoms: correctable ulnar deviation and periarticular swelling of the *MCP* joints of both hands gradually developed following repeated attacks of rheumatic fever with residual heart involvement.

Discussion

It is hoped that this account will stimulate a re-inquiry into the existence of chronic *secondary* polyarthritis, as the French and Germans call the chronic joint change following rheumatic fever

We believe that this is a real entity distinct from rheumatoid arthritis and that we have demonstrated it, at least in one case (O.L.). It is, however, we think, exceedingly rare, at least in this advanced form with bone destruction, and we find it difficult to believe that Kahlmeter's figures for incidence obtain in this country. Kahlmeter investigated the electrocardiographic evidence of myocarditis and the clinical presence of valvular lesions in a group of polyarthritis, 37 of whom were of secondary type, i.e. following and related to an earlier attack of rheumatic fever and 48 of whom were of primary type. His criteria were a prolongation of P–R interval to 0·20 or more, QRS changes, or inversion of T I. He compared this group with a control group of 65 acute rheumatic fever cases, 106 sub-acute, 68 non-rheumatic infections, 72 healthy people, and 45 non-cardiac patients, excluding all cases over 50 years, or with a nephritis, syphilis, or blood pressure above 160 mm., and in the group with chronic primary polyarthritis, all with previous rheumatic fever. It might be concluded from his figures that chronic secondary polyarthritis as a distinct entity closely allied to rheumatic fever is almost as common as primary chronic polyarthritis (i.e. rheumatoid arthritis).

It is possible that this is so, and that the variously higher figures for the incidence of rheumatic heart disease in our own and other autopsy series than in control series of the same age group are not due to selection but reflect a variable proportion of cases of chronic secondary polyarthritis in the various series. If this is really so (and we have no grounds for believing it), it should be possible to distinguish clinically, radiologically, and pathologically between the two types, on grounds other than those of Kahlmeter (presence of valve lesions and electrocardiographic abnormalities). Can we reconstruct a tentative picture of the syndrome that we must keep a look out for? From our own one probable and three more possible cases that we have cited in this category, the following features that might prove to differentiate it from rheumatoid arthritis proper are:

(*a*) There is a history of acute rheumatic fever attacks, usually multiple and distinguishable historically from acute rheumatoid only by the migratory nature of the initial polyarthritis, perhaps the character of the rash, the presence of chorea, the development of heart lesions, or the response to salicylates. Nodules have occurred.

(*b*) Recovery has been delayed and associated with stiffness of the *MCP* joints, but this may pass off or the patient may gradually slide into a state of joint deformity.

(*c*) The characteristic deformity is due to periarticular and fascial fibrosis rather than synovitis.

(*d*) It consists of flexion at the *MCP* joints with some periarticular soft tissue swelling over them and in the wrist region, together with ulnar deviation and/or subluxation affecting particularly the fourth and fifth fingers. This ulnar deviation is correctable by voluntary effort in the early stages. There may furthermore be a hyperextension at the *PIP* joints, although these are not themselves swollen.

(*e*) Tendon crepitus may be elicited (and in this connection we could cite cases of rheumatic fever with transient flexor tendon contractures associated with palmar nodules, as a probable preceding phase (e.g. Bywaters, 1949).

(*f*) The disease is relatively inactive, with a normal sedimentation rate and often little or no complaint of the joints, and in the early stages retention of normal functional capacity.

(*g*) Radiologically the earliest bone change is erosion of the metacarpal heads on the most palmar and radial part of their circumference in the anteroposterior projection, producing later a hook-like erosion.

The other end of this range of cases also may prove a diagnostic problem. In rheumatoid arthritis with valvular disease and evidence of pericarditis, the possibility of rheumatoid heart disease should be borne in mind, especially if there is a great deal of nodule formation. As this type is apparently so rare, however, the likelihood is that most such individual cases will prove ultimately to have rheumatic heart disease.

There remains the possibility (which we do not favour) that rheumatoid arthritis and rheumatic fever are variants of one disease entity. Both are comparatively common diseases and if this were so between-grades should be frequent: we think that the rare between-grades that are seen are spuri-

ous and that such cases will be found on fuller and adequate examination to fall clinically and pathologically into one of the several types we have described. However, as so many have commented, until the causes of one or both are known this is an occupation for theorists. In practice we know that rheumatic fever attacks the heart and rheumatoid arthritis the joints; the occurrence of rare combinations such as we have described scarcely affects the practical conduct of the physician but an adequate investigation of them may throw a great deal of light on the nosological status of this group of diseases.

Summary

On the basis of a necropsy series of 27 cases of rheumatoid arthritis and 4 cases of spondylitis ankylopoietica, the following three types of clinical relationship between rheumatoid arthritis and rheumatic fever are distinguished, besides uncomplicated rheumatoid arthritis alone and those presenting rheumatic heart disease alone.

(1) Rheumatoid arthritis with deformity of valves due to rheumatoid granulomata in the valve cusp and ring, and frequently accompanied by pericarditis. One such case is described and the close resemblance of pericardium and synovial membrane is pointed out.

(2) Rheumatoid arthritis developing in a person who has already had, usually during childhood, an attack of rheumatic fever which has left rheumatic heart disease.

(3) Rheumatic fever which has occurred several times and has left in its wake a chronic type of rheumatism affecting mainly the metacarpo-phalangeal joints with some pericardial swelling, ulnar deviation, and subluxation. Biopsies in two cases showed capsular fibrosis and normal synovial membrane. In one case, this type of " chronic secondary polyarthritis " had produced bone and cartilage erosions and in another probable case this had commenced to form characteristic hook-like deformity of the metacarpo-phalangeal heads. It is thought that it might be possible to distinguish these cases from more ordinary rheumatoid arthritis with coincident rheumatic heart disease on clinical grounds. A review of the subject is given and a history of the clinical confusion traced from the time of Jaccoud who first recorded this chronic type of post-rheumatic joint disease and left a clinical description as good as any subsequent account of the disease.

I am most grateful to my colleagues in the Departments of Medicine and Pathology at the Postgraduate Medical School of London and in the Canadian Red Cross Memorial Hospital, Taplow, for allowing me to see and cite their cases together with the pathological records and material. I am indebted also to Dr. Coghill who allowed me to see Case O.L., and to Dr. Francis Bach who furnished Figure 3. Mr. Wilmott took the microphotographs.

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ATEBRIN IN PAROXYSMAL TACHYCARDIA AND PAROXYSMAL AURICULAR FIBRILLATION

BY

F. VEGA DIAZ

From the General Hospital, Madrid

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There is a wide range of remedies available for the treatment of the paroxysmal arrhythmias, which comprise auricular and ventricular paroxysmal tachycardia and paroxysmal flutter and fibrillation. Although vagal stimulation by pressure on the carotid sinus or eyeballs sometimes stops paroxysmal tachycardia, it is not effective in auricular fibrillation. Again, trials have been made of many drugs which include strophanthus, quinine, and quinidine (sulphate and chloride), both natural and synthetic, potassium acetate, α-fagarin, acetyl-beta-methyl-choline, magnesium sulphate, doryl, prostygmin, carbachol, ipecacuanha, apomorphine, and atropin.

In recent years, Gertler *et al.* (1946–47) have employed atebrin in the treatment of paroxysmal arrhythmias with clinical and experimental results that have seemed encouraging but require confirmation. Our own experience, in this connection, is set forth hereafter.

Pharmacological Considerations

Gertler and Karp (1947) showed that atebrin, derived from *acridin*, could paralyze the inhibitor vagal fibres of dogs' hearts, thereby proving a certain parallelism with quinidine in its pharmacological action, since both inhibit cholinesterase (Wealsch and Nachmanson, 1944) and intensely depress the heart's excitability, an action also demonstrated experimentally by Chin (1937) and Harvey (1939). A paralysing action on the motor end-plate has also been described by these workers. Molitor (1941) described various alterations of the cardiac rhythm, including heart-block and ventricular flutter and fibrillation, through toxic doses of atebrin. In view of these similar pharmacological effects of atebrin and quinidine, Gertler and Karp (1947) inferred that the former should restore the sinus rhythm in patients with auricular fibrillation, and they proved this action experimentally on dogs.

Moreover, it was shown that atebrin was not toxic for the myocardium in anti-malarial therapeutic doses (Hecht, 1933; Gertler and Karp, 1947; Heimann and Shapiro, 1943; Smith and Stoeckle, 1946).

Gertler and Karp (1947) made preliminary trials by animal experiment and came to the conclusion that this medicine, given by intravenous infusion in doses of 2·17 mg. per kilo body weight, produced no cardio-toxic phenomena and was effective in stopping experimental fibrillation. Using atebrin subsequently clinically, they confirmed these conclusions with the qualification that larger doses might produce ventricular arrhythmias or heart-block as described by Molitor (1941). Smith and Stoeckle (1946) had previously shown that a massive dose of atebrin given intravenously had toxic effects on the heart-lung preparation in dogs. On the other hand, Gertler and Yohalem have explained this on the basis of atebrin in massive concentration being strongly acid and producing

effects similar to those of any other acid solution injected in the same way (Gertler, Hoff and Humm, 1946; Gertler and Yohalem, 1947).

Gertler and Yohalem's first clinical paper proves the usefulness of atebrin in paroxysmal auricular fibrillation and supraventricular paroxysmal tachycardia in man, as a medicine comparable with quinidine; it also shows that the effect of intravenous injection of atebrin for auricular fibrillation in man is comparable to the results obtained by Gertler and Karp in experiments on animals. The similarity of action of atebrin and quinidine may be due to the characters of their chemical formulas. Recent investigations by Di-Palma and Lambert (1948) confirm the importance of the methoxy and dioxymethylenic groups in the action of anti-fibrillatory substances. These authors, studying the experimental fibrillation umbral in hearts under quinidine, cinchonine, α-fagarin, and N-methyl-dibenzil-amine found that, though one of these drugs—cinchonine—had no methoxy group, all of them possessed an evident anti-fibrillatory power. Cinchonine is almost as active as quinidine, and α-fagarin five times more so, but the authors fail to prove the anti-fibrillatory action of N-methyl-dibenzil-amine (a pressor substance of the sympatho-mimetic amine type) against the previous opinion of De Espanés *et al.* (1946). They only mentioned atebrin by the way, this drug also having a methoxy group in its formula. Agreeing with previous assertions of Dawes (1946), Di Palma and Lambert concluded that the methoxy group and the di-oxymethylenic group are of the utmost importance in the structure of anti-fibrillatory drugs and expect research along these lines will produce the ideal anti-fibrillatory substance whose pharmacological effects may be produced through the metabolism of muscular contraction. Possibly the finding of atebrin is a step forward in this direction.

Gertler and Karp point out that atebrin also has certain advantages over quinidine, of which most of the properties have been known since the work of Lewis (1925). Whereas clinical effects with quinidine are sometimes delayed five to ten hours (Wegria, 1942 and 1948), no doubt because of its staying in the cardiac muscle (Weissman, 1945), atebrin given intramuscularly in doses of 0·4 g. reaches a 60–220 mg. per litre of blood level within the first hour and, at the end of three hours, falls to 60–120 mg. (Shannon, 1944), and remains for a long time at 1 : 300,000 (Dikshit, 1939). Thus the maximum effects of atebrin are attained before three hours and can be maintained afterwards owing to its persistent retention in the organism; Molitor (1941) reported that one isolated dose took 7 or 8 days to disappear from the organs (the heart not being mentioned) and in some patients traces of it were found nine weeks later, owing to the cumulative tendency of the drug and its slow excretion (Dearborn *et al.*, 1943).

Although atebrin is not notably toxic for the myocardium it is not to be administered lightly. Its general toxic effects are well known (Temkin and Ramsey, 1944; Bispham, 1941).* These will not be dealt with here. However, since the doses suggested by Gertler and Yohalem are well under the toxicity level, its use is permissible and advisable for clinical trial. Using doses therapeutically effective though under the anti-malarial dosage, we only seriously suspected toxic phenomena in one case, whereas therapeutically effective doses of quinidine are frequently toxic (Vega Diaz, 1949; Maranon and Vega Diaz, 1948; Wegria and Nickerson, 1942).

Gertler and Yohalem (1947) state that according to Nahum *et al.* (1946) and Jervell (1946), the circular movement causing auricular fibrillation is due to the existence of an exciting factor, E, on which a vagal stimulation is superimposed (as recently confirmed by Schlichter, 1948), and that this so-called exciting factor may exist in many morbid processes such as thyrotoxicosis, acute infections, and stretching of the auricular fibres during the great dilatations of cardiac insufficiency (Best and Taylor, 1944). These authors conclude that, in the restoration of sinus rhythm in cases of auricular fibrillation, the intensity of these two factors is important. Thus in grave hyperthyroidism as in acute infections and in cardiac insufficiency, the anti-fibrillatory effect might be very poor and it is in such cases that Atebrin may be less useful. Gertler and Yohalem presented a case of paroxysmal auricular fibrillation and one of supra-ventricular paroxysmal tachycardia and stated

* See also Fourth General Report of the Malaria Committee of the League of Nations (1937). *Treatment of Malaria*, Bull. of Health Organ, League of Nations, **6**, 895.

that, when publishing the paper in question, they had nine other cases in their experience at Mount Sinai Hospital. In the case of auricular fibrillation they injected intramuscularly a dose of 0·6 g. atebrin in 10 c.c. novocaine at 1 per cent, sinus rhythm reappearing in two and a half hours' time. In a second attack of auricular fibrillation the same dose was repeated at intervals of 12 hours and the rhythm became normal two hours after the second injection. In these circumstances the authors gave 0·1 g. orally three times a day during ten days and once a day during three more, without any reappearance of arrhythmias. Their second case, in a paroxysm of infra-nodal tachycardia (referred to as supra-ventricular), was treated with 0·1 g. intravenous atebrin, sinus rhythm being restored 45 seconds after injection.

Case Reports

Using doses similar to those of Gertler and Yohalem, we have employed atebrin* in

4 cases of paroxysmal auricular fibrillation;
1 case of (infra-nodal) nodal paroxysmal tachycardia; and
1 case of variably occurring paroxysmal auricular flutter.

Case 1. A. C. R., aged 21. Isolated attacks of palpitation since the age of 15, lasting at first three to four hours, and only occurring under strain or emotion. Attacks occurring two or three times a year. Two months ago began to feel early-morning extrasystolic sensations and attacks of tachycardia were more frequent, being repeated up to four times daily and always beginning and ending suddenly. The last two attacks lasted 12 and 16 hours respectively and a sensation of precordial oppression came on four or five hours after start of each attack.

Clinical examination. Inspection and palpation of heart and major vessels revealed no abnormality. First sound at apex ill-defined.

Arterial pressure 122/65 mm. Heart radiologically normal.

Electrocardiograms: normal during phases of normal rhythm.

During one attack infra-nodal paroxysmal tachycardia (Fig. 1) appeared and was stopped by pressure on the carotid sinus. On another occasion when vagal stimulation proved inefficacious, three doses of 0·1 g. of atebrin were given intravenously at two-hourly intervals and exactly twenty seconds after the last injection the attack stopped. It was recorded electrocardiographically in transit to sinus rhythm. Later examination of this patient revealed the presence of hyperthyroidism.

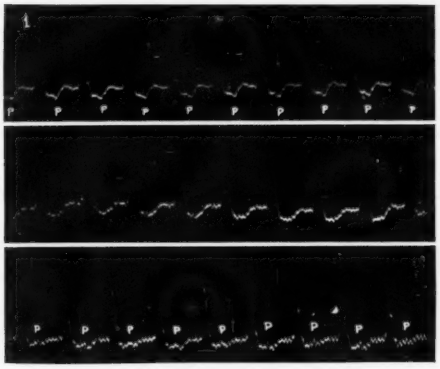
Case 2. O. G., aged 23. Always tended to have palpitations. Two years ago, in acute bout of alcoholic intoxication, had paroxysmal tachycardia lasting half an hour which was stopped with ouabaine. Before attacks, had extrasystoles; during the attacks, cold sweat and collapse, with livid appearance. Attacks began and ended suddenly.

Personal history. Rheumatic fever at 16. Afterwards some flitting rheumatic pains.

Clinical examination. The only outstanding feature was a systolic murmur in the aortic area during expiration and slight increase of the second sound at the same area. Blood pressure 120/70. Radioscopy showed a slight hypertrophy of left ventricle.

Electrocardiogram. In a curve recorded two hours before one of the attacks (Fig. 2) auricular extrasystoles were found and a slurring in the ascending limb of the R wave in lead I and in the descending limb of this wave in lead III. During the attack nodal paroxysmal tachycardia was demonstrated. A dose of 0·4 g. of atebrin was injected intramuscularly, and the attack ceased after five minutes. In previous attacks digitalis had failed and quinidine had caused deep disturbances of the ventricular complex when the dose reached 1·2 g. so that it had to be discontinued.

* In all our cases we have used Bayer's atebrin, in 0·1 g. and 0·3 g. capsules. When we want to give 0·4 g. we put the solution of one 0·3 g. and one 0·1 g. capsule in the same syringe; we have dissolved atebrin in 1 per cent novocaine solution for intramuscular injection and in distilled water for intravenous use.



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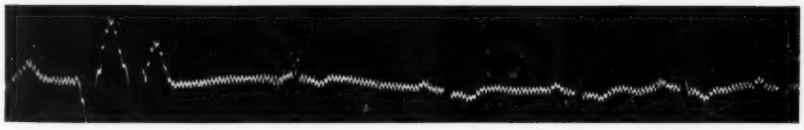

B

FIG. 1.—Case 1. (A) Attack of infra-nodal tachycardia. (B) 20 seconds after a third dose of 0·1 g. atebrin, intravenously.

Case 3. M. L., aged 59. Rheumatic fever in childhood, without relapses. For many years attacks of paroxysmal tachycardia, rather infrequent. Flatulence of large bowel with intermittent diarrhœa.

Clinical examination. Plethora. Soft presystolic murmur at apex. Marked meteorism. Arterial pressure 140/75 mm. Basal metabolic rate +40 per cent.

Radioscopy. Large globular heart, of slightly mitral shape; in right anterior oblique, slight deviation of the œsophagus by moderate dilatation of the left auricle.

Electrocardiogram. Between attacks: full-sized P waves; curves otherwise normal. In attacks: paroxysmal flutter-fibrillation (Fig. 3). 8 ml. cedilanid injected and 4 ml. twelve hours afterwards. Twelve hours later, the rhythm not having become normal, 0·6 g. atebrin was injected intramuscularly in 10 ml. 1 per cent novocaine solution; the attack was thus brought to an end after lasting seventeen hours. In both electrocardiograms the slanting S–T segments characteristic of digitalis effect were observed.

Case 4. J. R. de A. Productive tuberculosis of the right lung with marked fibrotic retraction of this hemithorax. One year before first examination there was a severe bout of arrhythmia, diagnosed as extrasystolic, which lasted six hours. A few days later there was a further attack, this time of paroxysmal arrhythmia, lasting several days and cut short with digitalis. Since then, attacks have always occurred following irregularity of the pulse and have been repeated every two or three months. The last one started one month before our examination and is still persisting. Slight cardio-respiratory insufficiency phenomena.

Clinical examination. Constitutionally normal; heart sounds intense; lessening of breath sounds in left hemithorax. Complete arrhythmia with high heart rate. Blood pressure 115/75. No passive congestion. B.M.R. +33 per cent.

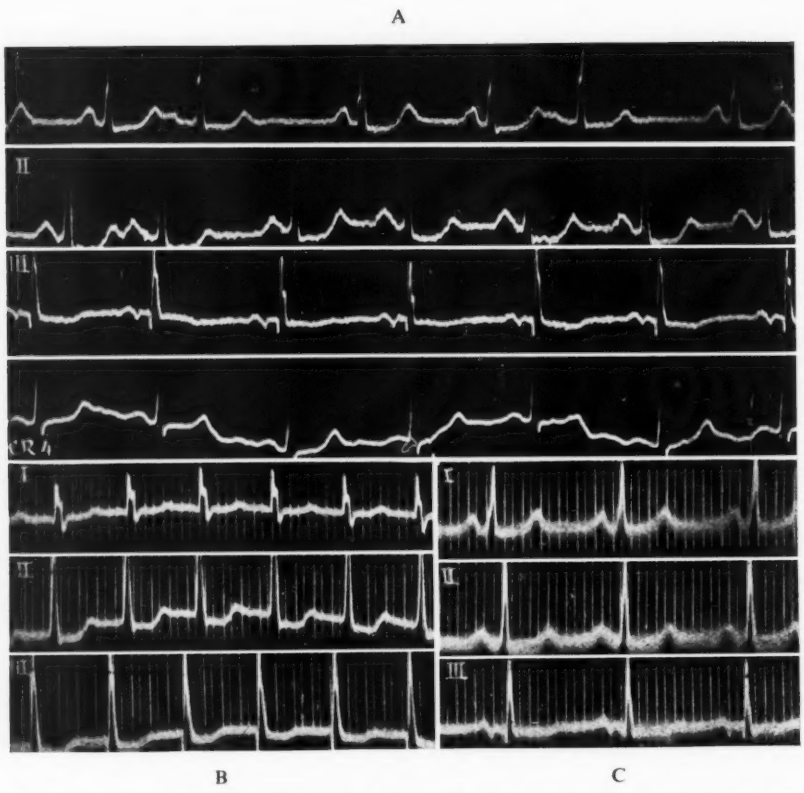

FIG. 2.—Case 2. (A) Electrocardiogram taken two hours before the attack recorded at (B). (B) Supraventricular tachycardia. (C) Normal rhythm ten minutes after an intramuscular injection of 0·4 g. atebrin.

Electrocardiograms. In the first curve, auricular fibrillation of right ventricular type (Fig. 4). Treated with quinidine sulphate; the rhythm became normal when 1·6 g. had been given. Relapsed 76 hours later; then treated with 0·1 g. intravenous atebrin, sinus rhythm being restored within three minutes.

Case 5. C. G. C., aged 28. Rheumatic fever when 10 years old. Residual slight effort syndrome. For the last five months paroxysmal tachycardia of increasing duration; from a few minutes at first to sixteen hours in the attack before last. They are bouts of auricular fibrillation with high ventricular rates. So far they have responded to quinidine sulphate.

Clinical examination. Short presystolic murmur at apex and ill-defined second sound at the pulmonary area. Harsh systolic murmur at the aortic area. Blood pressure 110/60 mm.

Radioscopy. Appearance of mitral and aortic disease without much cardiac dilatation, but with left ventricle hypertrophy.

Electrocardiograms. Curve between attacks of normal ventricular type without intracardiac conduction anomalies and with bicuspid P waves.

After one attack had lasted six hours, 0·1 g. atebrin was administered intravenously Three hours later, the attack persisting, the dose was repeated; a further dose three hours later still was

FIG. 3.—Case 3. (A) Paroxysmal flutter-fibrillation. (B) After digitalis treatment and intramuscular injection of 0·6 g. atebrin. Observe anomalies in S–T spaces, of digitalis type. See text.

given, but without success. Three days after the last dose of atebrin quinidine sulphate was administered and the attack stopped half an hour after the second dose of 0·4 g.

Case 6. F. P., aged 60. Treated jointly with Dr. L. Alzua of San Sebastian. The patient was plethoric. He had had hypertension for many years, with generalized arteriosclerosis. For some years past, there had been phases of paroxysmal auricular flutter lasting several days with rhythm alternating from 3 : 1 to 4 : 1, nearly always of the pure flutter type Digitalis medication had failed totally, even though the saturation stage had been reached (8 c.c cedilanid in one dose and 4 c.c. twelve hours later). In this patient a first dose of 0·4 g. intramuscular atebrin (administered thus for lack of intravenous capsules) resulted in a transient restoration of normal rhythm, the ventricular rate dropping to about 60 per minute. No electrocardiogram could be taken at the time. One hour later he relapsed into a state somewhat different from his former one, a flutter-fibrillation remaining with periods of impure flutter. A second dose of atebrin again altered the rhythm, which was maintained at 120 a minute during more than 24 hours; but it was found that

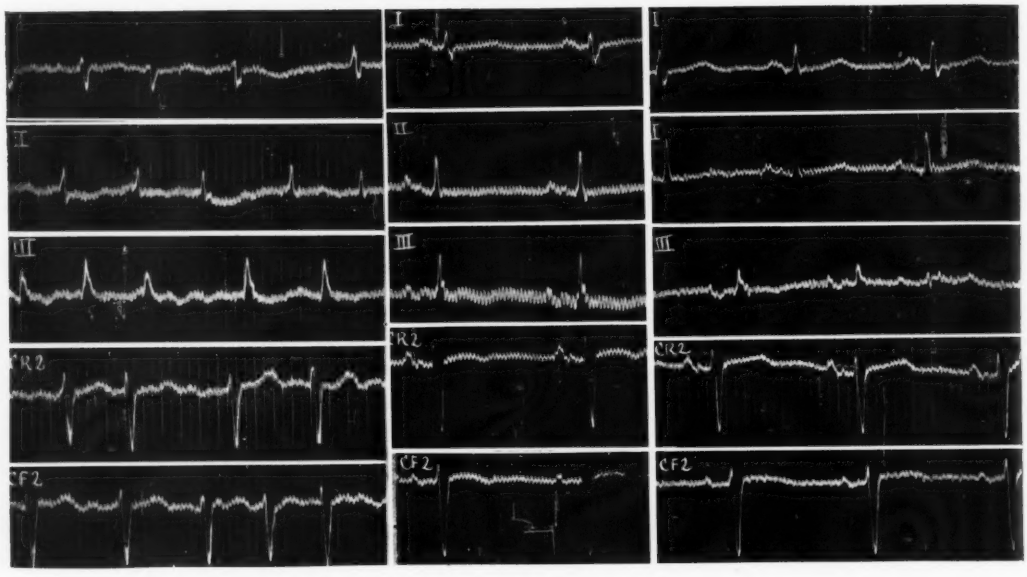

FIG. 4.—Case 4. (A) Paroxysmal auricular fibrillation with ventricular complexes of right type. Relapse of an attack previously stopped with quinidine sulphate. (B) Normal rhythm three minutes after an intravenous injection of 0·1 g. atebrin. There are post-therapeutic anomalies of the S–T spaces of the precordial leads, which may be due either to the quinidine or the Atebrin. (C) Normal rhythm maintained 48 hours after the previous record.

this apparently normal rhythm was, in fact, a pure flutter with 2 : 1 block and severe subjective troubles.

Not much can be inferred from this case, since we suspect that the flutter concealed a stable auriculo-ventricular block, with high ventricular rate associated with left ventricular insufficiency due to coronary sclerosis. The relevant figures are therefore omitted, but will be published with a later paper.

DISCUSSION

We have obtained good results in four of the six cases of acute tachycardial arrhythmia treated with atebrin. In the other two we failed, and in one of these there were possible complicating phenomena. These two cases, however, lead us to refrain from premature conclusions.

Of the patients relieved, two had paroxysmal tachycardia and the other two auricular fibrillation. We cannot, therefore, make any generalization as to the pharmacological effect of this drug in paroxysmal arrhythmia.

Of the cases of paroxysmal tachycardia, one which was clinically normal showed phases of transient increase of metabolism, suggesting that hyperthyroidism might be of pathogenic significance. In the other case, with slight rheumatic aortic stenosis, the attacks of auricular fibrillation coincided with phases of alcoholic intoxication; and in spite of the almost certain liver disorder due to alcoholism the drug acted rapidly. One of the known toxic effects of this drug is that on the liver cell, but the fact that the attacks were stopped even by rather large doses encouraged further use of this drug. In this case, digitalis had failed on two previous occasions and quinidine had once produced toxic electrocardiographic manifestations that made it advisable to stop this medication.

One of the cases of paroxysmal auricular fibrillation had a rheumatic mitral lesion, while in the

other case the heart was sound but with a marked cardio-respiratory syndrome due to pulmonary fibrosis. Both had a high B.M.R. which, in one (Case 3), was clearly due to hyperthyroidism. The other case was questionable because of the respiratory syndrome.

Nothing conclusive can be inferred from these four cases beyond a consideration as to the role of hypermetabolism. The excellent results obtained in these four cases from the use of atebrin do not seem to confirm the theory of Gertler and Yohalem as to the ineffectiveness of this drug in syndromes like hyperthyroidism in which the vagal influence is reduced. The only case of paroxysmal auricular fibrillation which did not yield to atebrin was, in fact, free from this disorder of metabolism.

Atebrin thus appears to be a useful drug for acute tachycardial arrhythmias, above all for those with a raised metabolic rate, whether or not this is due to hyperthyroidism (Vega Diaz, 1949; Maranon and Vega Diaz, 1948). This point is important since it is known that in hyperthyroidism anti-tachycardial drugs often fail, or must be given in maximum doses, or produce toxic phenomena (Maranon and Vega Diaz, 1948). In Case 3, relief was only obtained with atebrin, although there were clinical and electrocardiographic signs of digitalis saturation. It may be that the digitalis restored normal rhythm (the dose having been large enough to warrant this supposition), or the effect may have been due to the complementary action of the two drugs. This summation phenomenon is widely known and used in cardiological clinics,* but it frequently gives rise to similar doubts. The attacks may also have ended autochthonously. Nevertheless, the fact remains that in this case the paroxysm only stopped when atebrin was administered.

The two cases of failure deserve separate mention.

Regarding Case 5, atebrin was not efficacious although quinidine was. Previous attacks had been arrested by quinidine and it had to be employed again after several hours of unavailing use of atebrin.

Our sixth case, of paroxysmal auricular flutter with 3 : 1 and 4 : 1 auriculo-ventricular block, had great left ventricular stress of the common left bundle-block type, with clinical evidence of atheroma. Atebrin seemed to restore normal rhythm at a rate of 60 a minute without the transition being recorded electrocardiographically. One hour later impure flutter had set in. A second dose of atebrin produced tachycardia at the rate of 120 a minute—2 : 1 flutter with troublesome subjective phenomena. This case is one of atebrin failure in flutter, but at least it shows that the drug has an effect on cardiac rhythm.

SUMMARY

Six cases are presented of paroxysmal tachycardial arrhythmia treated with atebrin. In four of them (two of paroxysmal tachycardia and two of paroxysmal auricular fibrillation) the bouts were stopped in a striking manner. In the other two the drug proved ineffective, although one of these cases (paroxysmal auricular flutter) was difficult of interpretation. It is considered that atebrin is a useful medicament, especially in patients with a high B.M.R. or slight hyperthyroidism. It may be less dangerous than quinidine, although possibly of less potency and less efficacious when repeated.†

From these few observations no conclusive inferences can be drawn, but it does seem that atebrin possesses an anti-tachycardial and anti-fibrillatory action. Because of the quickness of its action and its sustained effect through its permanency in the body, atebrin may well be the remedy of choice in some cases, especially when the B.M.R. is somewhat high, since quinidine is much more rapidly eliminated and may be more toxic. With quinidine there is only a small margin between therapeutic and toxic doses, and these are sometimes the same; moreover, when it is toxic it sets up serious cardiac complications almost from the start, even with doses that are not large.

* To give only one example, it is unanimously recognized that carotid pressure after a dose of digitalis is efficacious to stop a paroxysm of tachycardia in which such treatment had previously failed.

† Since writing this paper we have been able to try atebrin in a further case of paroxysmal auricular fibrillation, without producing any effect whatever after three intravenous doses of 0·1 g. This makes us even more reticent than we were, notwithstanding the initial successes.

Atebrin, which is not toxic for the myocardium in therapeutic doses, gives a wide margin between therapeutic and toxic doses. Its effects are slow and general rather than cardiac, and this reduces the chances of emergencies, notwithstanding the retention of the drug in the system. This very retention, moreover, enables us to trust in the continuity of the effects even when it is not repeatedly administered; this cannot be said for the other anti-fibrillatory or anti-tachycardial drugs. This fact makes us consider that atebrin may, therefore, be useful in maintenance doses as a prophylactic medicament.

Further experience of success or failure must be awaited before a judgement can be formed as to the usefulness of this medication for acute tachycardia, its indications and its dosage.

NOTE: Since this paper was sent in a new publication by Gertler and Yohalem has appeared (*Amer. Heart J.*, **37**, 79, 1949), in which they again insist on the scantier success of atebrin in auricular fibrillation of hyperthyroid origin. Although working in a hospital department mainly engaged in endocrinology we have not been able to amplify our experience as regards atebrin in the last few months. We fully concur with all these authors' other data. In another paper of ours (Maranon and Vega Diaz, 1948) we have drawn attention to the possibility of some cases of hypermetabolism not being directly hyperthyroid, the thyroid intervening only as an interposed agent of hypothalamic regulation.

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AN RS–T PATTERN ASSOCIATED WITH MYOCARDIAL INJURY

BY

EMANUEL GOLDBERGER

From the Medical Division, Montefiore Hospital, and the Cardiographic Department, Lincoln Hospital, New York

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Normally, the RS–T segment may lie above, on, or below the base line. When it begins above the base line, it frequently dips sharply toward the base line, then ascends with a downward convexity to meet the peak of an upward T (Fig. 1). The lowest point, or nadir, of the RS–T is nearer to the beginning of the RS–T than to the peak of the T. In addition, the peak of the T is taller than the initial elevation of the RS–T. It may be difficult to separate sharply the end of the QRS complex from the beginning of the RS–T because the end of R may be slurred or notched (Fig. 1B).

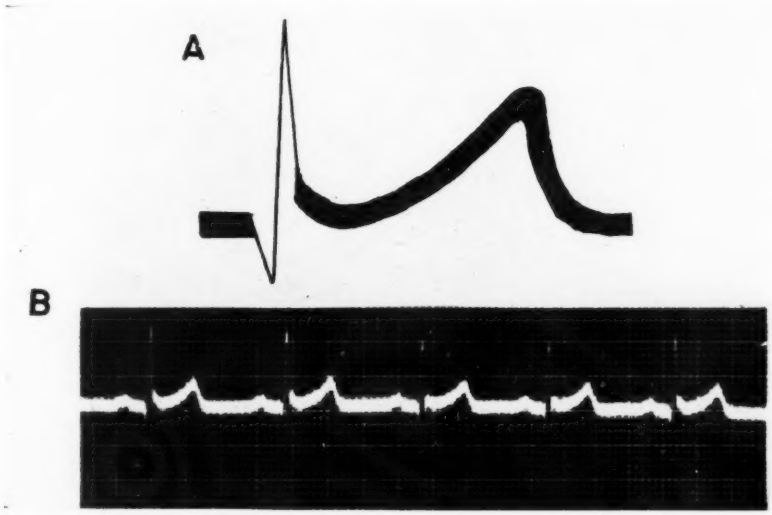

FIG. 1.—(A) Diagram of a normal, elevated RS–T segment. See text.
(B) An example of a normal elevated RS–T. Notice that the end of the R may be slurred or notched.

After myocardial injury, the RS–T segment not only becomes abnormally elevated (and depressed, depending on the lead taken), but it usually shows abnormal characteristics. Parkinson and Bedford (1928) have described the following three types of abnormal RS–T segments resulting from myocardial infarction.

(1) *The plateau RS–T* (Fig. 2A). Here, the RS–T segment begins above the base line, runs straight and horizontally, fuses with the T and descends gradually to the base line.

(2) *The dome-shaped RS–T* (Fig. 2B). Here, the RS–T segment begins above the base line and continues to rise with an upward convexity. As it begins to descend it fuses with the T.

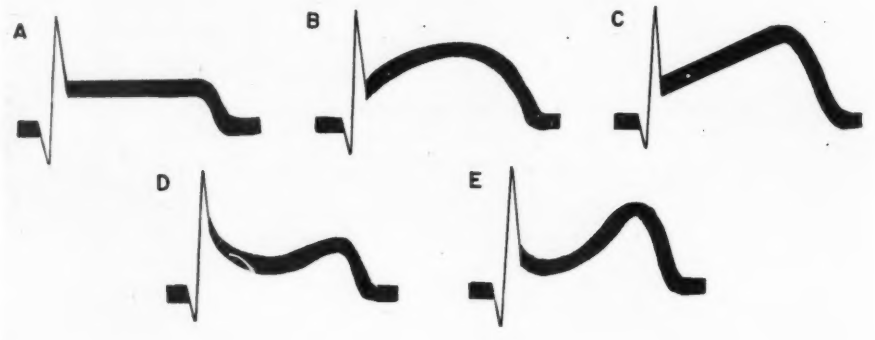

FIG. 2.—Diagrams showing abnormal, elevated RS–T segments. See text.
(A) Plateau RS–T. (B) Dome-shaped RS–T. (C) Obliquely elevated RS–T. (D) Crescent RS–T. (E) Abnormal elevated RS–T with a normal downward convexity.

(3) In the third type, the RS–T segment begins above the base line and continues to rise obliquely like an inclined plane. At its summit it fuses with the T and descends to the base line (Fig. 2C). Parkinson and Bedford did not use any descriptive term for this RS–T pattern, which, however, can be called, *the obliquely elevated RS–T.*

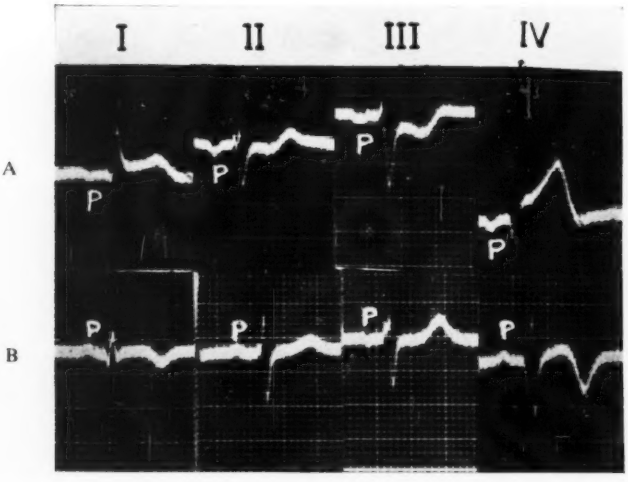

FIG. 3.—(A) Elevated RS–T segments with normal downward convexities after myocardial injury. The tracing was taken a day after the infarct occurred.
(B) This was taken a week later. The RS–T segments are now dome-shaped.

The elevated RS–T segment may also show a normal downward convexity after myocardial injury (Fig. 2E and 3A). In such cases, when the RS–T is not markedly elevated and when

abnormal Q waves are not present, it may be very difficult to determine whether the elevated RS–T is normal or abnormal. For this reason, we decided to study examples of myocardial infarction and pericarditis that showed elevated RS–T segments with downward convexities to learn whether such elevated RS–T segments differed in any way from a normal elevated RS–T.

Material and Results

The electrocardiograms of 160 cases of acute myocardial injury were selected at random from our files. These included 75 cases of anterior infarction, 75 cases of posterior infarction, and 10 cases of pericarditis. In a majority of these cases multiple unipolar præcordial leads and augmented unipolar extremity leads had been taken in addition to the standard leads.

For control purposes, 50 normal tracings with elevated RS–T segments were selected at random.

One hundred and twenty-seven of the 160 tracings of myocardial injury showed characteristic plateau, dome-shaped, or obliquely elevated RS–T patterns (along with other electrocardiographic evidence of myocardial injury).

Thirty-three tracings showed an abnormal elevation of the RS–T with a downward convexity in one or more leads. In 20 of these cases the abnormally elevated RS–T was similar to a normally elevated RS–T except for the degree of elevation (compare Fig. 3A, with Fig. 1B).

Thirteen tracings showed an abnormal, elevated RS–T which differed in shape from the normal; this we have called a *crescent RS–T*. The crescent RS–T has the following characteristics: it begins above the base line, descends in a gentle slope and then turns and rises to merge with the peak of an upward T. The result is to form an inverted dome or a crescent (Fig. 2D). The lowest point or nadir of the RS–T is equidistant from the beginning of the RS–T and the peak of the T. It may be difficult to separate the first portion of the RS–T from the end of the QRS complex, which may be thickened or notched.

In those leads that show reciprocal depression of the RS–T, the depressed RS–T may show an upward convexity (Fig. 5, lead aVL).

These 13 tracings with a crescent RS–T included nine cases of posterior infarction, two cases of anterior infarction, and two cases of pericarditis. Examples of the crescent RS–T are shown in Fig. 4, 5, 6, and 7.

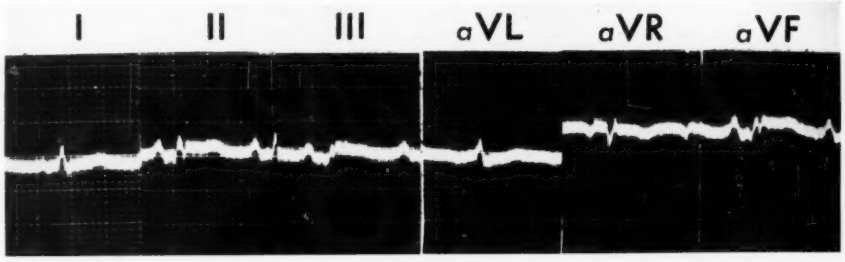

FIG. 4.—Crescent RS–T segments after myocardial injury from a case of posterior infarction. Leads II, III, and aVF are abnormally elevated. The crescent RS–T appears in leads II and aVF. Lead aVL shows slight reciprocal depression of the RS–T.

In Fig. 4, a case of posterior infarction, the crescent RS–T is seen in lead II and lead aVF.

In Fig. 5, a case of posterior infarction, the crescent RS–T is seen in lead III and lead aVF.

In Fig. 6, a case of pericarditis, the crescent RS–T is seen in lead aVF.

In Fig. 7B, a case of anterior infarction, the crescent RS–T is seen in lead I, lead aVL, and precordial leads V3 and V5.

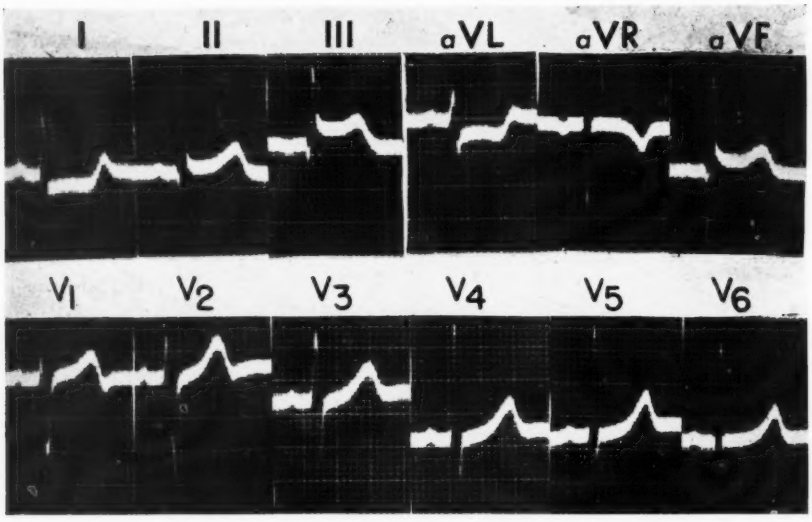

FIG. 5.—Crescent RS–T segments after myocardial injury, viz. posterior infarction. Leads II, III, and aVF show elevated RS–T segments. Crescent RS–T segments appear in leads III and aVF. Leads I and aVL show reciprocal depression of the RS–T. Notice that the depressed RS–T segments show an upward convexity.

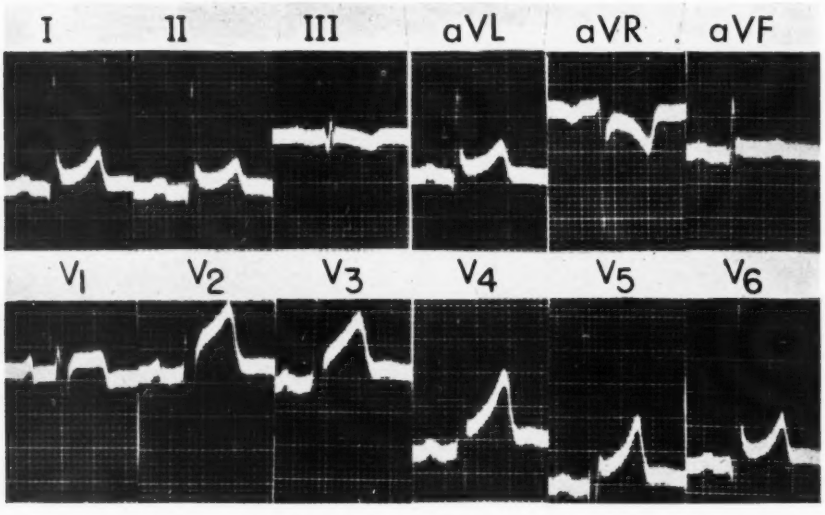

FIG. 6.—Crescent RS–T after myocardial injury, viz. pericarditis. Leads I, II, aVL, and aVF, and præcordial leads V4, V5, and V6 show elevated RS–T segments. Only lead aVF shows a crescent RS–T. Lead aVR shows reciprocal depression of the RS–T.

Discussion

All our cases that showed a crescent RS–T also showed other electrocardiographic signs of myocardial injury such as plateau, dome-shaped or obliquely elevated RS–T segments in one or more leads or abnormal Q waves, or marked reciprocal depression of the RS–T in one or more leads, or elevation of the RS–T that was abnormal according to statistical criteria.

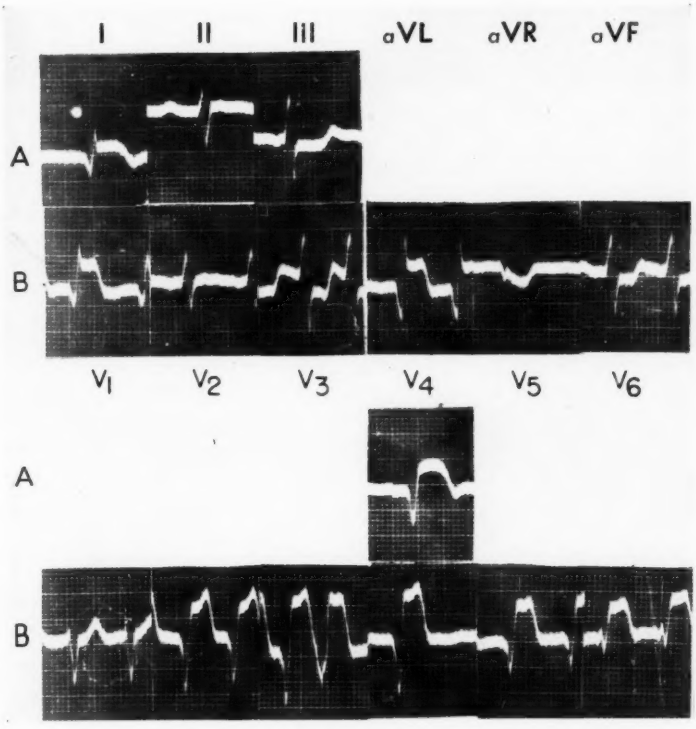

Fig. 7.—A case of anterior infarction.

(A) was taken a day after the infarct occurred. Lead I shows an abnormal Q and a plateau RS–T. Lead V4 shows an abnormal Q and a dome-shaped RS–T.

(B) was taken two days later. Crescent RS–T segments have appeared in leads I, aVL, and præcordial leads V3 and V5. Auricular fibrillation is now present.

None of our normal control cases showed a crescent RS–T. In order to check this further, we surveyed several hundred additional normal and abnormal tracings (excluding cases of myocardial injury), and were not able to find a crescent RS–T in any of this group. In this connection, a normal RS–T with a downward bowing should not be confused with a crescent RS–T. This might happen when a small R is associated with an upward T. Fig. 8, lead aVL, shows such an example. Notice that there is no elevation of the RS–T.

The downwardly convex and crescent elevation of the RS–T usually occurs in the early stages of myocardial injury, and as a deep, symmetrical T wave develops, the RS–T usually becomes dome-shaped (Fig. 3). However, the crescent RS–T may occur later than a dome-shaped or plateau or obliquely elevated RS–T.

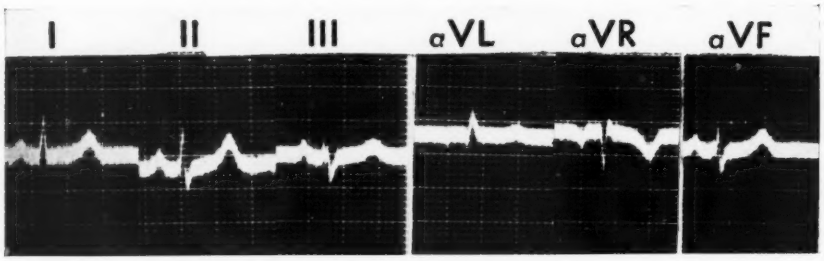

FIG. 8.—A normal electrocardiogram. In lead aVL, the RS–T segment superficially resembles a crescent RS–T.

CONCLUSION

It has been known that when myocardial injury occurs, the RS–T segment not only becomes elevated (and depressed) but that the elevated RS–T shows characteristic patterns, namely, plateau-shaped, dome-shaped, and obliquely elevated. However, an elevated RS–T with a normal downward convexity can also occur after myocardial injury. When such an RS–T is not markedly elevated or when other electrocardiographic signs of myocardial injury are not present it may be difficult to differentiate such an RS–T from a normal RS–T.

Examination of such elevated RS–T segments has shown that in a percentage of these cases the elevated RS–T not only has a downward convexity, but shows a characteristic "crescent" shape that does not occur normally. Further studies may prove that the presence of a crescent RS–T is of value in the diagnosis of myocardial injury even in the absence of any other electrocardiographic signs of myocardial injury.

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CONGENITAL HEART DISEASE ASSOCIATED WITH SUBDIAPHRAGMATIC LATERAL HETEROTAXY

BY

JOHN THOMSON

From the Department of Child Life and Health, University of Edinburgh

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Since congenital heart disease associated with subdiaphragmatic lateral heterotaxy is seldom reported, it is thought desirable to record the following two cases.

Case 1. W. J. This full-time male child was born spontaneously on August 12, 1947. It was a first pregnancy and the parents were unrelated. The birth weight was 6 lb. 9 oz. and when the child left hospital on the ninth day he appeared to be in good condition and weighed 6 lb. 11 oz. When three months old he was referred to the author as a possible case of congenital heart disease.

There was a history of frequent cough and circumoral cyanosis. Præcordial pulsation was apparent and a forceful heart beat was palpable in the fifth, sixth, and seventh left intercostal spaces as far out as the anterior axillary line. There was a harsh systolic murmur of maximum intensity in the same area. Radiological examination disclosed a grossly abnormal cardiac outline suggestive of imperfect intracardial septa. There was also disclosed a subdiaphragmatic lateral heterotaxy.

Though physical growth was a little retarded, his general development was satisfactory. At a year old there were six teeth erupted, he could walk but needed to hold on, and speech had begun. The features were somewhat florid. The weight was just over 17 lb. At eighteen months he could walk well, put two words together, was active and showed no undue signs of breathlessness. He always wanted to go to bed about six in the evening and slept soundly till seven the following morning. There was no clubbing of the fingers but the florid appearance was more pronounced. The weight was 22 lb. While radiological examination was being repeated at this time, barium was given. The œsophagus was to the right of a left aortic arch. There appeared to be gross enlargement of the right ventricle (Fig. 1).

The following electrocardiogram report was also obtained. "The heart rate is high, but fairly regular at approximately 140 a minute. The P waves are deeply inverted in lead I, shallow in lead II, upright in lead III. There is marked right axis deviation. The T waves are flat in lead I, upright in leads II and III. In the chest leads there are moderate R waves in V1 to V3 with deeper S. S is slurred in V1 and V2, of large amplitude in lead V3. T waves are high, upright and over 20 mm. in V2. In V4 to V6 there are short R and deep S waves. T is upright in V4, diphasic in V5, inverted in V6. Leads from the right chest, corresponding to V3, show R and S of nearly equal amplitude. T is upright. The lead from the right midclavicular line shows moderate R with short S. Leads from the anterior axillary and mid-axillary line on the right side show short R as predominant and sole initial deflection respectively. The leads from the right chest are of the type seen in a normal subject in leads from corresponding points on the left chest. Taken in conjunction with the appearance of standard lead I, these leads may be taken as highly suggestive of a true dextrocardia." (Fig. 2.) This is a most unusual electrocardiogram, as the heart seemed clinically and radiologically to be on the left.

FIG. 1.—Case 1. Aged 18 months. Note the difference in the levels of the diaphragm on the two sides.

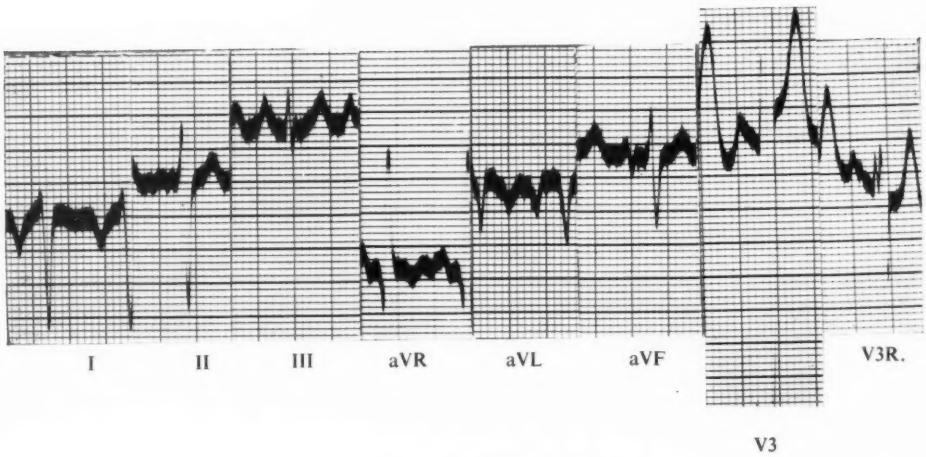


FIG. 2.—Electrocardiogram of Case 1.

Both parents have been examined radiologically and found to be normal. There is no history of congenital malformation on either line of descent.

Case 2. C. I. This girl came to my notice when, at the age of six years, she formed one of a group of prematurely born children whose physical and mental progress was under review. She was born of unrelated parents on March 24, 1943. It was a fourth pregnancy. During the pregnancy signs of secondary syphilis became apparent and although active anti-syphilitic treatment was instituted, the patient being in hospital for the purpose, the infant was born after only two weeks treatment. At the time of delivery the period of gestation was calculated as 38 weeks. The birth weight of the infant was 4 lb. 8 oz. She was breast fed and made good progress, being discharged on the fifteenth day when she weighed 4 lb. 9 oz. Anti-syphilitic treatment was carried out and the Wassermann reaction was negative at 8 months, doubtfully positive at 15 months, and negative at 3 years, when she was last seen at the venereal disease clinic.

Her physical measurements at the age of six were: weight, 30 lb.; height, standing 40 inches, sitting 23 inches; circumference at nipple level 20 inches, at umbilicus 17 inches. The superficial and deep reflexes were present and equal. The liver was palpable below the costal margin on the left side but as the diaphragm is lower on that side this is not necessarily an accurate estimate of liver enlargement. Epigastric pulsation was apparent and the apex beat was visible. Palpation showed it to be three and a half inches from the mid-line and in the sixth left intercostal space. The beat was forceful and was felt over a wider area than usual. A rough systolic murmur was heard in this area, and posteriorly to the left of the vertebral column. Radiological examination showed a large cardiac shadow of abnormal contour and a subdiaphragmatic lateral heterotaxy (Fig. 3).

The electrocardiographic report was: " Normal sinus rhythm, rate 100 a minute. P–R interval 0·16 second. The P waves are upright in lead I, biphasic in lead II, inverted in lead III. There is left axis deviation with prominent S waves in leads I and II. From the unipolar limb leads the heart is in a horizontal position. V1 shows polyphasic initial deflection and late activation of the underlying ventricle. T waves inverted. V2 shows tiny R, small S, tall R′ and moderate S′ with inverted T wave. In V3 to V6 R and S are approximately equal, with notching of the upstroke of R in V3 to V5. T waves are upright in V3 to V5, sharply inverted in V6. Additional leads taken from the right of the chest resemble aVR with diminishing height of R′ in V3R to V6R. The T waves are inverted in V3R to V5R, upright in V6R. The cardiogram shows the heart to be in the left side of the chest. There is evidence, however, of right ventricular hypertrophy and the chest leads do not show any evidence of left ventricular activity." (Fig. 4.)

The parents in this case are believed to be normal, but they have not been radiologically examined. There is no history of congenital malformation in the family history of either parent.

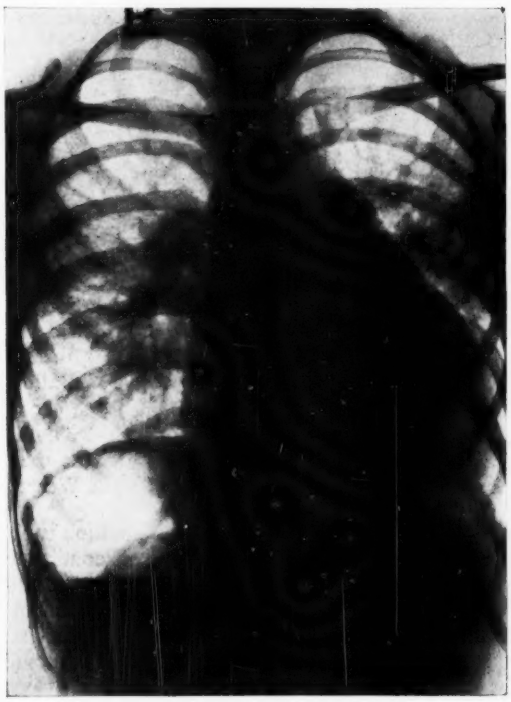
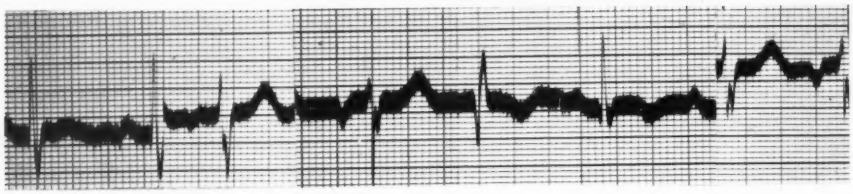


FIG. 3.—Case 2. Note the difference in the levels of the diaphragm on the two sides.



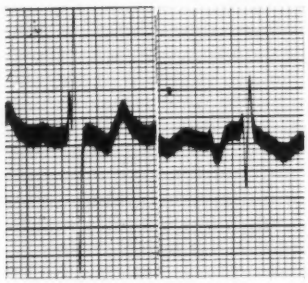


FIG. 4.—Electrocardiogram from Case 2.

DISCUSSION

In the course of an extensive survey of the literature on congenital dextrocardia, Lichtman (1931) made reference directly or indirectly to some cases where the occurrence of congenital heart disease, with the heart in the sinister position, was associated with some degree of subdiaphragmatic lateral heterotaxy. He gave the following references: Breschet (1826), Geipel (1899), Hickman (1869), Hingst (1901), Knape (1912), Lochte (1898), Miller (1925), McCrae (1906), Royer and Wilson (1908), Shaw and Blake (1924). He mentioned the case described by Griffith (1899) but confused the reference of this case with Griffith (1897). Though he does not mention it, he appears to have been aware of Marchand's (1883) publication. He noted another case by hearsay.

To this total of twelve recorded cases Forgacs (1947) added two cases of his own recording. He gave an incorrect reference for Marchand (1883) stating that it is quoted by Gruber (1865). Hardy (1948) reported two cases and in a further search found four other records, one of which (Clemente, 1931) is not available for consultation in this country. To this total of twenty cases may be added two now reported, and one each recorded by Grossmann and Mellor (1928), by Grieshaber (1936) and probably by Gardière and Damez (1935). Taussig (1947) mentions having seen the condition three times, but describes only the post-mortem findings in a single case. A doubtful case described by Henderson and Wright (1927) should also be noted.

Ætiology. The ætiology of this condition is obscure, though it has been suggested by Cockayne (1928) that situs inversus is a hereditary condition carried by a recessive gene. It would thus be more obvious in the off-spring of consanguineous marriage. In neither of the two cases now recorded is there any question of consanguineous marriage, nor is there any family history of congenital abnormality on either line of descent.

In his appraisal of the recorded cases, Forgacs (1947) claimed that of fourteen cases eight showed a transposition of atria. Because of this association he developed the original suggestion of Lochte (1898) also referred to by Pernkopf (1926) and advanced the view that the transposition of the atria is the result of an hypertrophy of the left horn of the sinus venosus instead of the

right horn, and that this in turn is caused by the transposition of the liver and ductus venosus which diverts most of the returning venous blood to the left horn instead of to the right as is usual.

This attractive theory does not rest on as good statistical evidence as Forgacs represented. From the eight cases that he claims as cases of transposition of the atria as many as four may be deducted. These are Miller (1925), McCrae (1906), Geipel, Case 3 (1899), and Forgacs (1947)*. Reference to Miller (1925) shows that no transposition of the atria was recorded. In the case of McCrae (1906) the heart was on the left but it was a mirror image heart of abnormal structure moved over to the sinister position. Transposition of the atria is recorded by Geipel, Case 3 (1899), but in this case the liver is on the right side. Forgacs' own case is omitted, for the diagnosis of transposition of the atria, though a good clinical one, is not supported by post-mortem evidence. If we limit our considerations to those cases that have come to autopsy, the theory is supported by four cases out of eleven.

Of the additional cases that have come to autopsy those reported by Taussig (1947) and by Pernkopf (1928) do appear to support the theory, but the case recorded by Hu (1929) is against it. Moreover, some cognizance must be taken of those cases of subdiaphragmatic lateral heterotaxy where it is claimed that the heart shows no abnormality. Geipel, Case 2 (1899), Goff (1927), Levrier (1932), and Buffé and Tanguy (1933) have each recorded one such case. Of these cases only that by Geipel had come to autopsy. It would appear that while the theory may have an application in the ætiology of some cases, where the condition arises in very early embryological life, its general application is not acceptable.

Diagnosis. In this syndrome the structural abnormality of the heart is usually a very prominent feature and is readily detected. This was so in the cases now recorded. So much is this so that a full clinical examination of the patient may not be made. Thus the accompanying subdiaphragmatic transposition of the viscera is overlooked. It is not without significance that the first ten cases to be recorded are spread over 87 years, from 1826 to 1912, while the next seventeen cases are reported in 37 years. Moreover, in British journals during 1947–49 three authors report two cases each. Thus the condition is probably not so uncommon as it seemed, and routine radiography in cases of congenital heart disease may result in more cases of this kind being recorded.

When it is observed clinically that the liver is transposed, it will be found that the lower edge of the liver is below the costal margin. In evaluating this sign it must be borne in mind that consequent upon cardiac development on the left side the level of the diaphragm on that side is lower than it is on the right side. Thus a normal sized but transposed liver will be at a lower level than one which is not transposed.

There are very few electrocardiographic records of this syndrome. Those which are published are confined to the standard leads, I, II, and III and a comparison of the recorded cases shows no uniform pattern. This is in keeping with the wide variety of abnormality in structure that has been found at autopsy in these cases. Because of the scanty information available it was felt desirable to record a fuller cardiographic investigation in these two cases. The two records obtained show very different patterns. The record of Case 1 is almost unique in that a cardiographic record of dextrocardia was obtained from a case in which the heart is, on clinical examination, found in the sinister position and with the apex beat palpable on the left side. It is to be noted that in order to exclude the possibility of error this was repeated on a different occasion on the same apparatus and with the same result. Grieshaber (1936) recorded an inverted electrocardiogram in the case he reported—a girl, aged eight years. In the case recorded by Shaw and Blake (1924) a dextrocardia electrocardiogram was obtained, but it is very doubtful if this should be grouped with the others, for consideration of the radiological findings suggests that this is a dextrocardia with the heart in the mid-line position. A somewhat paradoxical situation is seen in the case recorded by Henderson and Wright (1927): this 15-year-old boy, who had a pigeon chest,

* Dr. Forgacs still thinks he is correct about Geipel, Case 3, and there is no question that the heart was on the left in McCrae's case, but Thompson's interpretation seems correct. Editor.

was in an advanced state of congenital heart disease when he was seen by the authors. The left border of cardiac dullness was at the left nipple line and the right border at the right nipple line, while the greatest cardiac impulse was felt on the right side. Cardiac action was irregular and cardiographic examination showed this was probably due to fibrillation. A clinical diagnosis of dextrocardia was suggested but was not confirmed by the electrocardiogram.

Prognosis. The prognosis in this syndrome is undoubtedly the prognosis of the particular structural abnormality of the heart present in each case. This is well exemplified by the range of age which has been recorded. Grossmann and Mellor's patient was alive and 55 years old when reported, while in other cases, Marchand and Knape, the condition was not compatible with an independent existence for more than a few days.

Summary

Two cases of subdiaphragmatic lateral heterotaxy associated with congenital heart disease, the heart being in the sinister position, are recorded. In one of these, however, an electrocardiogram indicative of dextrocardia has been obtained.

It is suggested that the condition is not so uncommon as the few reported cases would suggest.

The nature of the deviation from the normal will largely depend upon the stage of intrauterine development attained before the start of the abnormal development. The nature of the abnormality varies from case to case.

A list of the twenty-five reported cases is given.

The electrocardiograms in these two cases were made at the Royal Infirmary, Edinburgh, and it is a pleasure to acknowledge the report in Case 1, received from Dr. I. G. W. Hill, and in Case 2 from Dr. D. Haig.

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* Case records are included in these papers.

CARDIAC CATHETERIZATION IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE *

BY

H. E. HOLLING AND G. A. ZAK *

From the Clinical Research Unit and the Cardiac Department, Guy's Hospital

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Cardiac catheterization is now a recognized method of clinical investigation and in recent years has been applied to the diagnosis of malformed hearts (Cournand *et al.*, 1949; Warren *et al.*, 1946; Groom *et al.*, 1948; Handelsman *et al.*, 1948; Dexter *et al.*, 1947; Bing *et al.*, 1947; Taylor *et al.*, 1948; Burchell *et al.*, 1948; Geiger *et al.*, 1946; Brannon *et al.*, 1945; Howarth *et al.*, 1947; Baldwin *et al.*, 1946; Soulie *et al.*, 1949). So far we have used this method on a group of 70 patients with a wide range of cardiac malformations. Here we attempt to evaluate the method as a diagnostic procedure, using the published results of other workers to supplement our own experience.

Cases Investigated

The cases were selected from a large number sent to Guy's Hospital mainly with a view to surgical treatment of their condition; they were under the care of Dr. Maurice Campbell, Mr. R. C. Brock, and Dr. Charles Baker, and clinical diagnoses were often discussed together. Patients with congenital heart disease often have multiple cardiac malformations of which one may be judged as functionally the most important, and in the table below they are listed under what appears to be the chief lesion. Thirty-six were over 15 years of age, twenty-two between the ages of 10 and 15, and twelve between the ages of 5 and 10 years.

Diagnosis	Number of Cases
Fallot's tetralogy	29
Pulmonary stenosis with closed ventricular septum	9
Pulmonary or tricuspid atresia	8
Transposition of the great vessels	4
Eisenmenger's complex	2
Patent ductus arteriosus	3
Isolated atrial septal defect	1
Truncus arteriosus	2
Lutembacher's syndrome	1
Ebstein's disease	1
Partial dextrocardia	3
Diagnosis uncertain	5
Pulmonary hæmangioma	2

At the end of the paper the results of catheterization of 18 illustrative cases are given, with explanatory notes intended to show how the general principles of interpreting results apply in particular cases. The diagnosis of some of these cases, in spite of angiocardiography and cardiac

* Work undertaken on behalf of the Medical Research Council. G. A. Z. was in receipt of a personal grant from the Medical Research Council.

catheterization, is still in doubt, but they have been included to represent problems that arise in practice. Several of the cases have been or will be discussed elsewhere (Allanby and Campbell, 1949; Baker *et al.*, 1949; Brock, 1948; Campbell and Hills, 1950). We have not attempted to catheterize all the cases admitted, because we find the procedure too time-consuming to be used in this way. It requires a full day's work for two investigators and a technician, and the co-operation of the X-ray staff for at least two hours. Moreover, the investigation is not without danger to the patient, who in any case is likely to find it an uncomfortable experience. We have therefore restricted its use mainly to those where the clinical diagnosis was in doubt, or where it seemed important to obtain the information that cardiac catheterization can yield.

Methods

The methods used do not differ materially from those of other workers and we comment only on points that seem important.

Sedation and anæsthesia. It is known (Hickam *et al.*, 1948) that anxiety on the part of the patient may increase the cardiac output without a parallel increase in oxygen consumption, thus decreasing the arteriovenous oxygen difference. Moreover, breath holding, crying, or struggling may materially alter the intracardiac pressures and gaseous content of the blood. It is important, therefore, that so far as possible the patient should remain under basal conditions throughout the catheterization. It is not easy to achieve this, particularly with children, because the method requires that the patient lie on the X-ray table for at least an hour. Moreover, the passage of the catheter into the heart often provokes tachycardia and sometimes extrasystoles, and in some patients manipulation of the catheter in the right ventricle causes a complaint of soreness under the sternum. We found that to engage the patient in easy conversation throughout the procedures is the best way of ensuring equable conditions. It is certainly undesirable to discuss technical points in the hearing of the patient. One to three grains of phenobarbitone were given about two hours before the start to adults and children down to the age of 8 years. Younger children, with one exception, required an anæsthetic. For this we first tried trilene or paraldehyde, which were recommended by the anæsthetists as being the safest agents, but their use disturbed the subsequent blood gas determinations. We have since found avertin satisfactory, given per rectum in a dose of 0·125 g. per kg. about half an hour before the insertion of the catheter. When deeper unconsciousness was required, avertin was supplemented with pentothal (about 0·15 g.). Though deepening of the anæsthesia probably altered the condition of the patient, it seemed preferable to risk this rather than to withdraw blood samples from a crying or struggling child.

Catheterization. The Cournand catheter was introduced into a cubital vein draining into the basilic system. The catheter sizes used ranged from 7 to 10, but usually an 8 or 9 was employed. A number of difficulties were met with during catheterization. It is inadvisable to try to force a catheter into a vein too small to accommodate it comfortably. In one instance when we attempted this an extensive thrombosis of the vein followed. On occasion the vein appeared to contract strongly, gripping the catheter and making its passage difficult. Usually in the experience of others and ourselves this can be avoided by gentle and smooth manipulation of the catheter. This happened once when the catheter tip was at the level of the outer border of the first rib, and for an hour and a half the catheter could neither be advanced nor withdrawn. Then following the injection of 1·5 ml. of 1 per cent procaine, through and alongside the catheter, and the application of hot water bottles to the arm, the catheter became free.

Either arm has been used for the insertion of the catheter, but in cases with a right-sided aortic arch it has seemed easier to enter the superior vena cava from the left, probably because of the more favourable angle between the left innominate vein and the superior vena cava. In one such case the catheter could not be advanced into the superior vena cava from the right in spite of a prolonged trial, but from the left arm this was achieved without difficulty.

On several occasions during the exploration of the right atrium for suspected septal defects

the tip of the catheter re-entered the superior vena cava and so formed a loop in the atrium. This has given rise to anxiety on the part of the operator because pushing the catheter caused the tip to move further into the vena cava, and pulling it caused the tip of the catheter to become wedged in the opening of the superior vena cava. On each occasion gentle manipulation of the catheter released it within a minute or two.

Since in our experience embolism has followed catheterization (see later) we emphasize the need for strict precautions against the formation of thrombi within the catheter or damage to the endocardium. The heparin saline drip (3000 units heparin per litre of normal saline) should be checked frequently, especially when entering chambers in which the blood is under high pressure, when it may be necessary to raise the saline reservoir. Manipulation of the catheter when inside the heart and great vessels, especially in the left ventricle, should be gentle to minimize the risk of trauma to the endothelium with subsequent thrombus formation. Cleaning the catheter should begin immediately after it is withdrawn.

Location of the catheter tip. In dealing with abnormal hearts in which unusual communications or obstructions may exist between the various chambers, it is important to locate the tip of the catheter as precisely as possible. The value of the lateral position should be remembered.

Fluoroscopic observation should start from the moment the catheter enters the thorax. The X-ray screening time has, however, to be limited, and in accordance with the measurements of Hills and Stanford (1950) we endeavoured not to exceed 25 per cent of the erythema dose. For us this meant about 20 minutes' screening time, though the diaphragms of the apparatus were adjusted to give as small a field as was required for directing the catheter tip within the heart. It is permissible to extend the screening time by 25 per cent when necessary for the completion of an important case.

Frequent measurement of intracardiac pressure is a great help in locating the tip of the catheter. For this purpose we have used saline, aneroid, and Hamilton manometers (Hamilton, 1934). The saline manometer is unsatisfactory mainly because of the slowness with which it reaches equilibrium, particularly when blood has passed into the catheter. The aneroid manometer requires the movement of only a small volume of fluid through the system before equilibrium is reached and so records quickly, but like the saline manometer it does not record systolic and diastolic pressures. However, the mean pressure is usually sufficient for diagnostic purposes, and because the aneroid manometer is so simple to use it can be generally recommended. Since it is not unlikely that evidence of value for diagnosis may be derived from a study of the form of the intracardiac pulse tracings, we have also used a Hamilton manometer with optical recording.

To aid in locating the catheter tip it is an advantage to ascertain the oxygen content of the blood samples while the catheterization is in progress. With this object some workers have arranged to have the blood analysed as it is taken so that the results may be known before the catheter is withdrawn, and further samples taken if necessary. We have not been able to do this, but undoubtedly it would be of great value. Wood *et al.* (1948) have described a photoelectric apparatus that may prove useful. Using this, the oxygen saturation of blood withdrawn from the catheter can be estimated almost as soon as it is taken, and samples from different parts of a cardiac chamber or chambers can be compared; and if they vary considerably, as many samples as necessary can be taken to estimate the average oxygen saturation of blood in the particular chamber.

The catheter sometimes enters the coronary sinus from the right atrium, but with experience this is quickly recognized and corrected; the following points are important. (1) As the catheter passes along the narrow coronary sinus it follows a fixed path and the curved tip cannot be turned around as when lying in the ventricle. (2) The catheter may appear as if its tip is about to pass into the pulmonary artery and occasionally as if it had entered the left branch of the pulmonary artery, but it always comes to a full stop within the cardiac shadow. (3) Although the catheter tip looks as if it is in the ventricle the pressure recorded is as low as in the atrium. However, if the catheter is advanced until it blocks the cardiac vein the pressure rises towards ventricular pressure (60/16 mm. Hg in Case 13, Fig. 12). Bing (1949) gives a record of the fall in pressure as the catheter

is withdrawn from blocking the cardiac vein. (4) The blood samples withdrawn from the coronary sinus are of a very low oxygen content (20 to 30% saturated).

Estimation of blood oxygen content. Blood samples from the catheter were withdrawn into vaselined syringes, and kept in them in the dark and in ice water until their oxygen content could be determined in a Haldane blood gas apparatus (Douglas and Priestley, 1948).

We found. as did Wassermann *et al.* (1949) and other investigators, that the oxygen content of the blood sometimes decreases if the blood is allowed to stand at room temperature. Our observations suggest this is not constant, for the blood sometimes shows only a negligible fall after standing at room temperature for 4 to 5 hours. In other cases, however, the blood oxygen content may show a considerable drop within an hour. In our experience the addition of sodium fluoride (0·6 mg./ml. blood) does not prevent the loss of oxygen. It is, however, greatly slowed by keeping the blood syringe in iced water, and kept in this way there is no material loss of oxygen over a period of 6 hours. For example, arterial blood was taken and the oxygen content (measured within 10 minutes of withdrawal) was found to be 15·4 ml./100 ml. (81% saturation) : one-half of the sample was kept in iced water, the other at room temperature (21° C.), and in all 13 estimations of oxygen content were done in the next 6 hours; these showed that the oxygen content of the blood kept in iced water remained steady for 6 hours at 15·4 to 15·3 ml. oxygen per 100 ml. but the oxygen content of that kept at room temperature slowly fell over 5½ hours to 14·6 ml. oxygen per 100 ml.

The blood was kept in the dark in order to prevent the formation of methæmoglobin, which is liable to form when blood is exposed to light.

Complications of Catheterization

Cardiac arrhythmias. Tachycardia up to 140 a minute in children may occur during catheterization, and is best avoided by the methods described under sedation. When the catheter tip is in the right ventricle the patient may be disturbed by extrasystoles but we have seen no harm come from them and our practice is to forewarn the patient and to reassure him that they are not of importance. Johnson *et al.* (1947) describe the onset of a paroxysm of auricular tachycardia or of 1 to 1 flutter which lasted for two hours after passing of a loop of catheter through the tricuspid orifice. Dexter *et al.* (1947) report auricular fibrillation in two of their patients with spontaneous restoration of normal rhythm within half an hour. Ventricular fibrillation is presumably a possibility though it has not been recorded.

General reactions. During the insertion of the catheter two of our female patients fainted, showing a cold, pale, sweating skin and a slow pulse; this occurred though they were supine and not complaining of any pain or discomfort. Several patients, especially when the catheterization has been prolonged, have complained of nausea immediately after the withdrawal of the catheter, and for the next five or six hours have felt very tired. Three children vomited immediately after and became temporarily more cyanosed; they also were extremely fatigued. Since any increase in the degree of the anoxia of these patients is dangerous, we have always had means of administering oxygen at hand.

Thrombosis and embolism. Localized thrombosis of the vein where the catheter was inserted often occurs, but it seldom extends far up the vein. Cournand (1949) finds that thrombosis is more likely to be limited if the incision is made at least 5 cm. distal to the opening of a branch vein into the basilic system.

It is generally held that cardiac catheterization is a safe procedure in man, and so far as we are aware there is only one reported case in which it is possible that catheterization had given rise to fatal thrombosis and embolism (Johnson *et al.*, 1947). The child died of an unspecified cause one month after catheterization and an unsuspected thrombus was found in the right atrium, inferior vena cava, and iliac and renal veins. Presumably the thrombosis had arisen at the site of the insertion of the catheter into the saphenous vein, or perhaps at the base of one of the tricuspid valves to which it was attached. Kinney *et al.* (1945) subjected the hearts of dogs to " traumatic "

catheterization for short periods and subsequent pathological examination of the hearts and great vessels showed no lesions attributable to the procedure. On the other hand some members of the same group later reported verbally endocardial lesions in dogs after catheterization of the pulmonary artery (Goodale *et al.*, 1947). Goodale had found mural thrombi and subendocardial hæmorrhages in the hearts of dogs that had been catheterized. These lesions were found to be more distinct when the animals were sacrificed more than 24 hours after the catheterization, and perhaps this may be the reason for the conflicting descriptions. In our experience with cases of congenital heart disease, cardiac catheterization is not without danger to the patient. Symptoms and signs indicating pulmonary or systemic thromboses or emboli have developed within 14 days of catheterization in no less than 6 of the 70 cases here reported. Details of these cases are as follows:

(1) O. D., aged 23 years (Case 9 of the appendix), a case of Eisenmenger's complex developed (the day after catheterization) an extensive thrombosis of her brachial vein. Seven days later she complained of pain in her chest and coughed up blood-stained sputum.

(2) C. L., aged 7 years (Case 13 of the appendix), had an unusual malformation of the heart described there. She was deeply cyanosed and bedridden, and was the most severley incapacitated of the children we have examined. Immediately after the withdrawal of the catheter she vomited and rapidly became unconscious and stopped breathing. Artificial respiration and oxygen were given for several minutes before consciousness returned. The next day she coughed up bloody sputum and remained critically ill for a fortnight. Having apparently recovered from the catheterization and a subsequent angiocardiogram, she died suddenly about seven weeks after the catheterization. No evidence of presumed pulmonary infarcts or of intravascular thrombi was found at necropsy.

(3) and (4) J. C. and R. C., aged 8 years, Fallot's tetralogy and tricuspid atresia respectively. Both complained of pain in the chest a few hours after catheterization, became dyspnœic and more cyanosed. J. C. had blood-stained sputum. They were nursed in an oxygen tent for a few days till they recovered.

(5) B. H., aged 10 years, a case of transposition of the great vessels. During catheterization the aorta was entered a number of times. About 8 hours after the catheterization he developed pyrexia, headache, and increasing drowsiness. The next day he was semiconscious, had neck rigidity, and a positive Kernig's sign. Lumbar puncture showed the cerebrospinal fluid to be under pressure and to contain blood. Several days later he also had diarrhœa. Chemotherapy was given from the start of his symptoms, but it was 3 weeks before he was well again. This unexpected sequel was thought to be the result of intravascular thrombosis.

(6) L. H., aged 19. Case described in detail (Baker *et al.*, 1950). One week after catheterization he developed sudden pain in both calves and died with bilateral gangrene of the legs 10 days later. At necropsy he was found to have the abnormality of the tricuspid valves known as Ebstein's disease. A partly organized thrombus was found on the septal wall of the left ventricle, which the catheter had entered via an atrial septal defect. In both popliteal arteries emboli were found, which had presumably originated from the intracardiac thrombosis.

Even without catheterization, thromboses and emboli may occur in these patients and at necropsy vegetations are often found on the deformed valves and edges of septal defects. In view of this tendency to spontaneous thromboses it is perhaps not unexpected that it should sometimes follow cardiac catheterization. To reduce the likelihood of endothelial damage we prefer to use the thinner and more flexible catheters, even though they are more difficult to direct in the heart.

The Interpretation of the Results of Blood Gas Estimations

The clinical differentiation of congenital heart disease may be uncertain because of the frequent occurrence of multiple defects. It is in this field that cardiac catheterization is being applied extensively, for by its use the presence of certain malformations may be proved. If, for instance, the catheter passes through a septal defect the fact can be recognized on the X-ray screen, or if the catheter is passed in to the pulmonary artery the stenosis can be recognized by the fall in pressure as the catheter tip passes through it. Often, however, direct proof is not obtained, though evidence of the defect may be found indirectly from comparison of the oxygen content of blood from the great vessels and chambers of the right heart.

An atrial septal defect with an arteriovenous shunt will result in blood in the right atrium being more oxygenated than blood in the venæ cavæ, or a patent ductus arteriosus will result in the blood

in the pulmonary artery being more oxygenated than in the right ventricle. Blood may flow either into the right or the left heart, and while an arteriovenous shunt would cause an increase in the oxygen content of the right heart blood, a venoarterial shunt would have no such effect. In practice it is not always easy to say whether an increase in oxygen content of the blood from right atrium, ventricle, or pulmonary artery indicates an admixture of oxygenated blood through a septal defect. This is because there are considerable variations in oxygen content of right heart blood, even in hearts with no septal defects or other abnormal communications. It is, therefore, important to know these variations so that the diagnosis of a septal defect may be made with more confidence.

Comparison of Blood from the Venæ Cavæ and Atrium

The difference in oxygen content that may occur between the blood of the venæ cavæ and the right atrium in the absence or presence of atrial septal defects is shown by the data from our own cases and those of other workers in Fig. 1, 2, and 3. The cases without atrial septal defect include not only malformed hearts, but also acquired heart disease and normal hearts. The diagnosis of an atrial septal defect, and whether the shunt through it was venoarterial or arteriovenous, was made on good clinical evidence, and in some cases confirmed by examination of the heart after

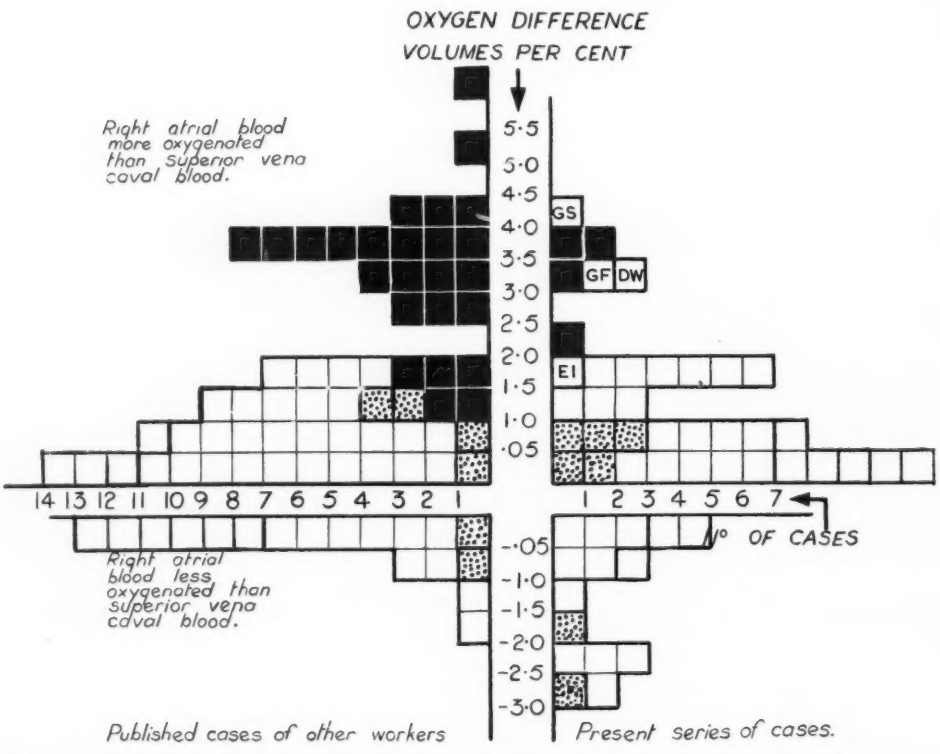

Fig. 1.—Differences in oxygen content (volumes per cent) of superior vena caval and right atrial bloods in 111 patients. The white squares represent cases with no atrial septal defect, black squares with an atrial septal defect through which a predominantly arteriovenous shunt occurs, and stippled squares with an atrial septal defect through which a predominantly venoarterial shunt occurs. The significance of the initialled squares is given in the text.

death. Cases in which the diagnosis of atrial septal defect was made largely or solely on the comparison of the oxygen content of blood samples could not, of course, be included in this series.

In Fig. 1, 2, and 3, the cases without atrial septal defect are shown as white squares, those with an atrial septal defect and a predominantly venoarterial shunt as stippled squares, and those with a predominantly arteriovenous shunt as black squares. The four lettered squares refer to cases that are discussed below.

Superior Vena Caval and Right Atrial Blood (Fig. 1)

Fig. 1 shows that in two-thirds of 95 patients with no atrial septal defect the oxygen content of right atrial blood exceeds that of superior vena caval blood, and that the difference may be as much as 2·0 volumes per cent. Of the other one-third with oxygen content of blood in the atrium lower than that in the superior vena cava, the majority show a difference of no more than 1 volume per cent, though this may reach as much as 3 volumes per cent. It follows that the diagnosis of an atrial septal defect with an arteriovenous shunt can only be made on the comparison of the oxygen content of blood samples if that from the right atrium exceeds that from the superior vena cava by more than 2 volumes per cent.

Using the standard of 2 volumes per cent a septal defect with arteriovenous shunt will be recognized in the large majority of cases; but a few, in which the difference lies between 1 and 2 volumes per cent, will be missed.

In those cases of atrial septal defect with a venoarterial shunt, the difference of oxygen content between superior vena caval blood and right atrial blood lies as would be expected, within the range of those with no atrial septal defect.

Inferior Vena Caval and Right Atrial Blood (Fig. 2)

Most workers have compared only superior vena caval and right atrial blood. Dexter *et al.* (1947), however, took blood samples from a few centimetres below the diaphragm and found that such blood from the inferior vena cava had a uniformly higher oxygen content than that from the superior vena cava or atrium. They believed that this was largely due to the influence of renal vein blood and abandoned the use of blood from the inferior vena cava for comparative purposes, relying solely on the comparison of right atrial and superior vena caval bloods. We have taken inferior vena caval samples routinely from a point just below the diaphram and find that the oxygen content is often, though not always, higher than that of atrial blood. Thus Fig. 2 shows that of 55 cases with intact atrial septa, in 34 the inferior vena caval blood was more oxygenated than that of the atrium, usually the difference was within 1 volume per cent, but reached as much as 3 volumes per cent. On the other hand, in 21 cases the inferior vena caval blood was less oxygenated than atrial blood; in most cases the difference was no more than 1 volume per cent, but exceptionally it was as great as 3 volumes per cent.

It is clear that if inferior vena caval blood is used for comparative purposes a higher oxygen difference (as much as 3 volumes per cent) must exist before a diagnosis of atrial septal defect can be made, and also that in a greater proportion of cases the diagnosis would be missed than when using superior vena caval blood.

It will be noted that in cases with a venoarterial shunt through the atrial septal defect the oxygen difference of inferior vena caval blood and atrial blood lies within the normal range.

Consideration of the oxygen content of inferior caval blood further demonstrates that (1) the vessel may contribute a stream of relatively oxygenated blood to the right atrium, (2) that for comparative purposes it would be better to use samples of both superior and inferior caval bloods, and to compare the mean of these two with that of the atrium.

Comparison of Right Atrial and Mean of Superior and Inferior Vena Caval Blood Samples (Fig. 3)

The difference in oxygen content of right atrial blood and the mean of inferior and superior vena caval blood (caval blood) in 84 patients is seen in Fig. 3. In 29 cases the right atrial blood was

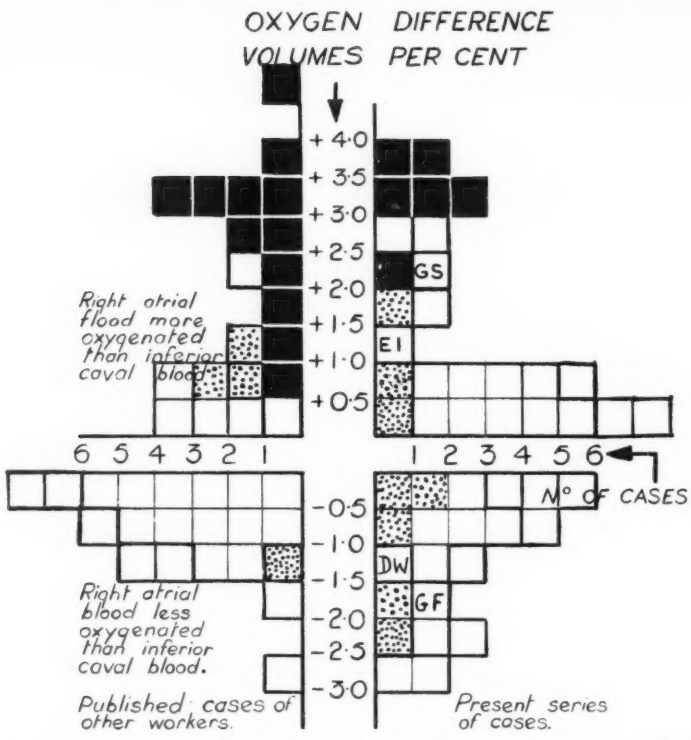

FIG. 2.—Differences in oxygen content (volumes per cent) of inferior vena caval and right atrial blood in 89 patients. White squares represent cases with no atrial septal defect, black squares cases with an atrial septal defect through which a predominantly arteriovenous shunt occurs, and stippled squares with an atrial septal defect through which a predominantly venoarterial shunt occurs.

more oxygenated than caval blood, in most cases by less than 1 volume per cent, and exceptionally by 1·5 volumes per cent. On the other hand, in 25 cases it was less oxygenated than atrial blood, in most cases by less than 1·5 volumes per cent, but exceptionally by as much as 2·5 volumes per cent. In all the cases of atrial septal defect with an arteriovenous shunt, the atrial blood was more than 2 volumes per cent higher in oxygen content than the mean of the superior and inferior caval bloods; so that taking the mean gives a better separation than if either the inferior or superior vena caval blood is used alone for comparison. In two of our cases, G. F. and D. W. (CB08 and O207) there was no reason to think that there was an atrial septal defect with an arteriovenous shunt. In these cases the right atrial blood sample was found to be 3·7 and 3·3 volumes per cent higher than that of the superior vena cava (Fig. 1), but in both the inferior vena caval blood had a considerably higher oxygen content than the atrial blood (Fig. 2). Fig. 3 shows that if the mean of the vena caval blood samples is taken in these two cases the oxygen difference between this and the right atrial blood falls within the range of cases without an atrial septal defect.

In Fig. 3 it is shown, as in previous figures, that when the shunt through an atrial septal defect is venoarterial the difference in oxygen content between caval and right atrial blood lies within the normal range. There is one exception in our cases, which was shown at necropsy to have an atrial septal defect so large that the two atria formed almost one chamber.

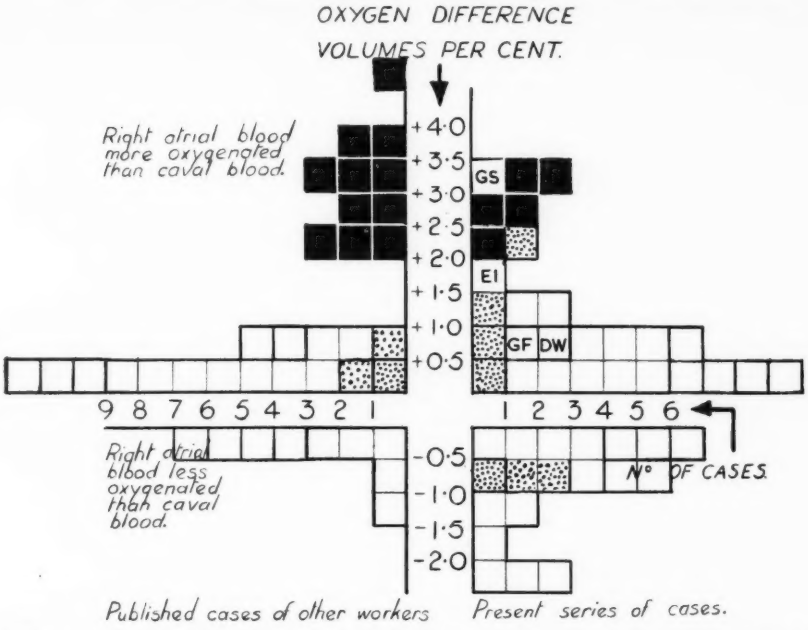

FIG. 3.—Difference in oxygen content between right atrial blood and the mean of the oxygen contents of the inferior and superior vena caval bloods in 84 patients. The white squares represent cases with no atrial septal defect, black squares cases with atrial septal defect through which a predominantly arteriovenous shunt occurs, and stippled squares cases with an atrial septal defect through which a predominantly venoarterial shunt occurs.

COMPARISON OF RIGHT ATRIAL AND RIGHT VENTRICULAR BLOOD SAMPLES

In Fig. 4 are shown the variations in oxygen content of right atrial and right ventricular blood in 49 cases considered to be without a ventricular septal defect and 98 with a presumed ventricular septal defect. In cases without ventricular septal defect the oxygen content of blood from the right ventricle may differ from that of the right atrium by $\pm 1{\cdot}0$ volumes per cent, and seldom more. This finding is not unexpected since blood in the right atrium, derived from superior vena cava, inferior vena cava, and coronary sinus is not uniformly mixed. Warren *et al.* (1945) showed that samples of blood taken from the right atrium might differ in oxygen content by as much as 2·3 volumes per cent. On the other hand, the blood in the right ventricle is better mixed so that samples taken from different parts of the ventricle differ by less than 1·0 volumes per cent. It follows, therefore, that when comparing the oxygen contents of blood samples from the venæ cavæ and right atrium it is useful also to compare the oxygen content of the atrium against that of the ventricle. If this is done the finding of an oxygen content of blood in the right atrium higher than the mean of the oxygen contents of caval bloods may arise (*a*) because the caval blood samples are not uniformly mixed and the catheter has withdrawn a sample derived mainly from the inferior vena cava, or (*b*) because the catheter had withdrawn a sample derived from an influx of highly oxygenated blood from the left atrium. If the high oxygen is due to (*a*) then the right ventricular blood should have a lower oxygen content than that of the atrial sample and should be about the mean of the caval samples. If the high oxygen content is due to (*b*) then the ventricular sample should also have a higher oxygen content than the mean of the caval samples. There are exceptional cases which do not fit into this conception ; for example in Case 2 (G. S., Fig. 1, 2, and 3) the right atrial sample

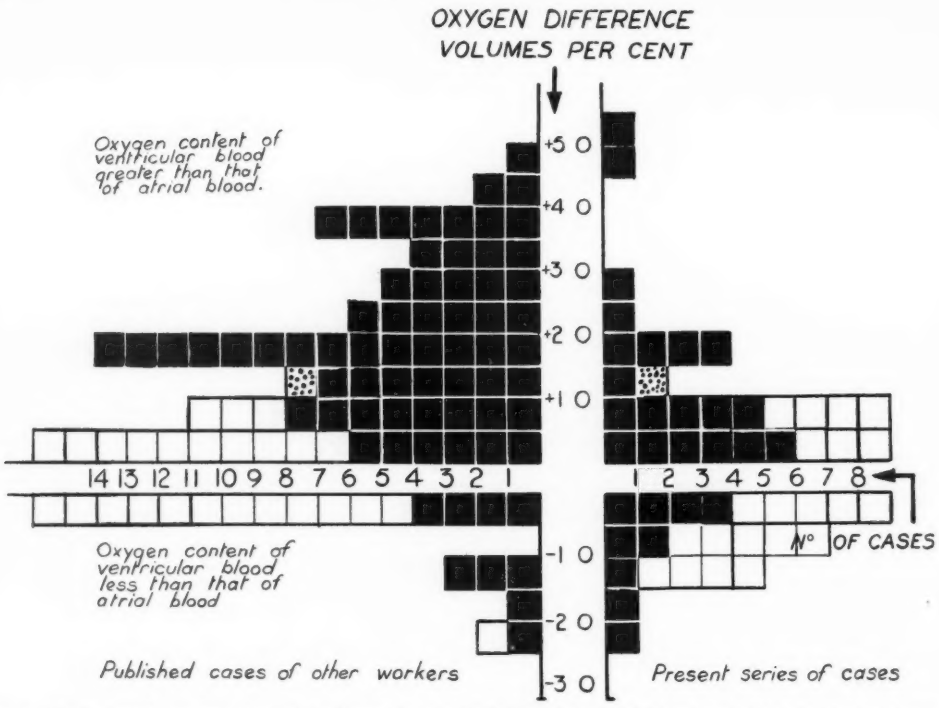
OXYGEN DIFFERENCE
VOLUMES PER CENT
Oxygen content of ventricular blood greater than that of atrial blood.
+5 0
+4 0
+3 0
+2 0
+1 0
14 13 12 11 10 9 8 7 6 5 4 3 2 1
1 2 3 4 5 6 7 8
N° OF CASES
Oxygen content of ventricular blood less than that of atrial blood
-1 0
-2 0
-3 0
Published cases of other workers
Present series of cases

FIG. 4.—Difference in oxygen content (volumes per cent) between right atrial blood and right ventricular blood in 147 patients. The cases with ventricular septal defects are indicated by black squares, those with intact ventricular septums by white squares. The two stippled squares indicated that in two cases of patent ductus arteriosus in which probable pulmonary regurgitation had resulted in an increase in the oxygen content of right ventricular blood. The square indicating that the oxygen content of the ventricular sample was 2 to 2·5 volumes per cent less than the atrial sample represents a case of atrial septal defect in which the atrial sample had presumably been taken close to the defect.

was 3·5 volumes per cent higher than that of the mean of the caval blood samples and 2·5 volumes per cent higher than that of the inferior vena caval sample; this seems to point to an influx of blood through a septal defect. Nevertheless, the blood from the right ventricle was of considerably lower oxygen content than right atrial blood. A possible explanation of the case is that when the right atrial sample was taken the tip of the catheter lay close to a small atrial septal defect, and so withdrew blood of a high oxygen content. We have not been able to prove that such an atrial septal defect was present. In a second and similar case, E. I., with Fallot's tetralogy, the difference between caval and right atrial bloods was 1·7 volumes per cent, indicating a probable atrial septal defect (Fig. 3). In this case the right ventricular blood was nearer that of the atrium in oxygen content, which would also support the diagnosis of an atrial septal defect. However, at necropsy no atrial septal defect was found (Case P061). The explanation of these findings is unknown.

Of the 98 cases with a ventricular septal defect, the difference between right ventricular and right atrial blood oxygen content was greater in 55 than in cases without ventricular septal defect. It is clear, therefore, that only about one-half of the cases of ventricular septal defect can be recognized by a higher oxygen content of the ventricular blood. It is to be noted that this increase in oxygen content occurred in spite of the fact that in almost all these cases the predominant shunt was from right to left ventricle. This is because of turbulence in the neighbourhood of the defect.

A high oxygen content of the right ventricular blood may be brought about not only by a septal defect, but also by regurgitation of blood through the pulmonary valves in cases of patent ductus arteriosus. This is clearly displayed by Cournand's (1949) Case 7, where the blood from the right atrium contained 10·6 volumes per cent oxygen, that from the right ventricle 12·5, and that from the pulmonary artery 14·2. After ligature of the ductus arteriosus the oxygen content of the right ventricle and pulmonary artery fell to the same level as that of the blood in the right atrium. The same phenomenon possibly accounts for the findings in the two cases of patent ductus arteriosus, indicated by stippled squares in Fig. 4, in which the oxygen content of the ventricular blood exceeded that of the atrial blood by 2·0 to 2·5 volumes per cent.

Comparison of Right Ventricular and Pulmonary Blood Samples

Fig. 5 shows the difference in oxygen content between right ventricular and pulmonary artery bloods in 82 patients. Thirty-three cases were considered to have neither ventricular septal defects

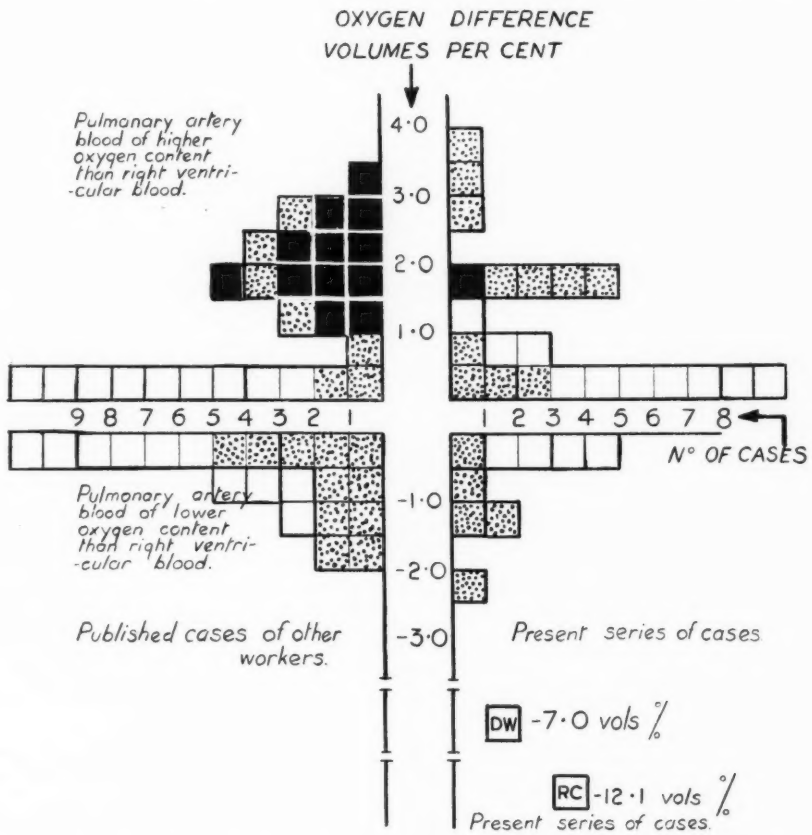

FIG. 5.—Difference in oxygen content (volumes per cent) of right ventricular and pulmonary artery bloods in 82 patients. White squares represent cases with no ventricular septal defect or patent ductus arteriosus, black squares represent cases with a patent ductus arteriosus, and stippled squares cases with a known ventricular septal defect. The significance of the two squares labelled D.W. and R.C. is given in the text.

nor patent ductus arteriosus. In the large majority the oxygen content of the right ventricular and pulmonary artery bloods differs by no more than 0·5 volumes per cent, and in only two by little more than 1·0 volumes per cent. In all 13 cases with a patent ductus arteriosus the difference in oxygen content was more than 1 volume per cent. Of the 34 cases with a ventricular septal defect but no patent ductus arteriosus, there are 11 with the pulmonary artery samples more than 1 volume per cent higher than that of the right ventricle. The explanation of this is probably that the defect is high in the ventricular septum so that the mixture of blood occurred in the region of the infundibulum and not in the main chamber of the ventricle from which the sample was taken. Whatever the reason it is clear that a higher oxygen content of the pulmonary artery blood may arise either from a patent ductus arteriosus or a high ventricular septal defect. A third possible cause of the oxygen content of the pulmonary artery blood being higher than that of the ventricular blood is pointed out by Dexter (1947). If the catheter is pushed too far into the pulmonary artery it may occlude the branch in which it lies so that when a sample is withdrawn oxygenated blood is aspirated from the pulmonary capillaries. This may be the explanation of the high oxygen content of the pulmonary artery blood reported by Soulie *et al.* (1949) in two cases in which there was neither a patent ductus arteriosus nor a septal defect. For this reason all our samples from the pulmonary artery have been taken not further than one inch past the bifurcation.

There are 10 cases in which the oxygen content of the pulmonary artery blood is more than 1 volume per cent lower than that of the right ventricle. This is difficult to account for, but since all but one of these cases had pulmonary stenosis this may have been a factor. A further clue is given by considering the two cases D. W. and R. C., in which the pulmonary artery blood sample was as much as 7 and 12 volumes per cent lower than that of the right ventricle. In both these cases there was probably a very gross stenosis of the pulmonary artery because the catheter seemed to be gripped in the orifice, and when it was withdrawn a sense of release of grip was obtained. Also in another (Case 7), a sample taken when the catheter had been in the pulmonary artery about five minutes was 29 per cent saturated with oxygen, but after another minute or two a second sample showed the saturation to have fallen to 15 per cent. These findings suggest that the catheter had materially obstructed the pulmonary orifice, reducing the amount of blood passing through the lungs and exaggerating the venoarterial shunt, thus increasing the patient's anoxia. The patients made no complaint whilst the catheter was in the pulmonary artery, and the darkness of the X-ray room prevented us from seeing an increase in cyanosis.

Calculation of Blood Flows and Shunts

In normal hearts the cardiac output can be calculated with a fair degree of accuracy by the Fick principle, using the oxygen consumption and the difference in oxygen content of arterial and mixed venous blood. It is clear that in malformed hearts calculation may be liable to error because of the existence of shunts. Nevertheless, in most instances an estimate may be made of the blood flow through the pulmonary artery and through the aorta, and thus of the volume of any shunt present. The pulmonary blood flow is calculated from the oxygen consumption and the difference in oxygen content between pulmonary venous and pulmonary artery blood, aortic blood flow is calculated from the oxygen consumption and the difference in oxygen content of arterial and mixed venous blood. It is usually easy to obtain a satisfactory sample of arterial blood but in malformed hearts it is not always easy to obtain equally satisfactory samples of mixed venous or pulmonary artery blood.

Mixed venous blood. In a heart with no arteriovenous shunts the blood from the outflow tract of the right ventricle can be regarded as mixed venous blood. In many malformed hearts with which we have dealt, right ventricular blood is not acceptable as mixed venous blood because of admixture of oxygenated blood either in the atrium or ventricle. In only 6 of 18 cases shown in the appendix could the right ventricular blood be regarded as free from admixture with arterialized blood. When blood from the right ventricle cannot be accepted as mixed venous blood, most authors, and we ourselves, have used a blood sample from the right atrium, provided there was no

evidence of an arteriovenous shunt through an atrial septal defect. If there was evidence of arterial admixture we have used the mean of the oxygen contents of the superior and inferior vena caval blood as representing that of mixed venous blood. This, however, is not altogether satisfactory because it is not known what volume each vena cava contributes to the blood entering the atrium, and the contribution to the mixed venous blood made by the coronary sinus and other veins entering the right atrium is neglected.

Pulmonary artery blood. Two factors may result in an unsatisfactory sample of blood being obtained from the pulmonary artery. If the catheter blocks the branch of the pulmonary artery in which it lies so that oxygenated blood is drawn from the lung capillaries the oxygen content of the blood sample will be unduly high. If the catheter obstructs even for a short time the stenosed pulmonary orifice the oxygen content of the sample of blood obtained may be unusually low. The presence of a ductus arteriosus makes it almost impossible to obtain a sample on which the estimation of the pulmonary blood flow can be reliably based. An approximation can be made by taking, as Cournand (1949) does, one sample from the artery and one from each main branch.

A further difficulty arises in many cases of suspected pulmonary stenosis when it is not possible to introduce the catheter into the pulmonary artery. In such cases blood from the right ventricular outflow tract is used as the best approximation. It is obvious from Fig. 5 that this would give rise to no great error, except when the ventricular septum is defective. For example, in Case 9, which showed the greatest difference between pulmonary artery and right ventricular blood (+4 volumes per cent) the pulmonary artery blood flow calculated on the pulmonary artery sample was 2 litres a minute per square metre, whereas when calculated on the right ventricular sample the pulmonary artery blood flow was 1·3 litres, or 35 per cent less. Apart from this case and those of patent ductus arteriosus, the two results never differed by more than 15 per cent when we have been able to calculate the pulmonary blood flow from both right ventricular and pulmonary artery samples. Even taking the higher of the two calculated flows the pulmonary blood flow in pulmonary stenosis was still reduced below normal.

Pulmonary venous blood. It is necessary in cases of cyanotic congenital heart disease to obtain evidence of the degree of saturation of the blood in the pulmonary veins, for though in patients with normal hearts it may be accepted that arterial blood gives a measure of pulmonary vein blood saturation, in cases of malformed hearts with a venoarterial shunt this assumption cannot be made. Bing *et al.* (1947) in 4 cases of Fallot's tetralogy obtained blood from a pulmonary vein by passing a catheter through an atrial septal defect and in each case the pulmonary vein blood was 95 per cent saturated. A few other isolated case reports have since been published which agree with this finding, and we have obtained pulmonary venous blood in 5 cases, either through an atrial septal defect or from a pulmonary vein draining into the right atrium. In each case we have found it to be 95 to 97 per cent saturated. None of these had signs of congestive failure or of pulmonary disease, either of which might have interfered with oxygenation of blood in the lungs; all had polycythemia, a factor that in the past has been thought to result in impaired oxygenation of blood passing through the lungs. It seems justifiable to conclude that in cases of congenital heart disease, provided that there is no congestive failure or pulmonary disease, the blood becomes 95 per cent saturated in passing through the lungs.

The Application of Cardiac Catheterization to the Diagnosis of Congenital Heart Disease

Fallot's tetralogy. The success of the operative treatment of Fallot's tetralogy has led to emphasis of the physiological features of the malformation (reduced pulmonary blood flow and venoarterial shunt) rather than the four anatomical features described by Fallot.

Operative treatment is directed towards increasing the blood flow through the lungs which is reduced by the pulmonary stenosis. Before operation one should, therefore, know that the pulmonary blood flow is in fact reduced below the normal. In the majority of cases clinical methods suffice to establish this, but there remain a few in which the reduction of the pulmonary blood flow

is in doubt. It is to be remembered that slighter degrees of stenosis of the pulmonary orifice do not necessarily result in a materially reduced pulmonary blood flow (see Case 5).

Cardiac catheterization can demonstrate the pulmonary stenosis by showing a reduction in blood pressure as the catheter tip passes from the right ventricle into the pulmonary artery (Fig. 6). By correlating the position of the catheter tip with the changes in pressure it can sometimes be shown whether the stenosis is at the pulmonary valves or in the infundibulum.

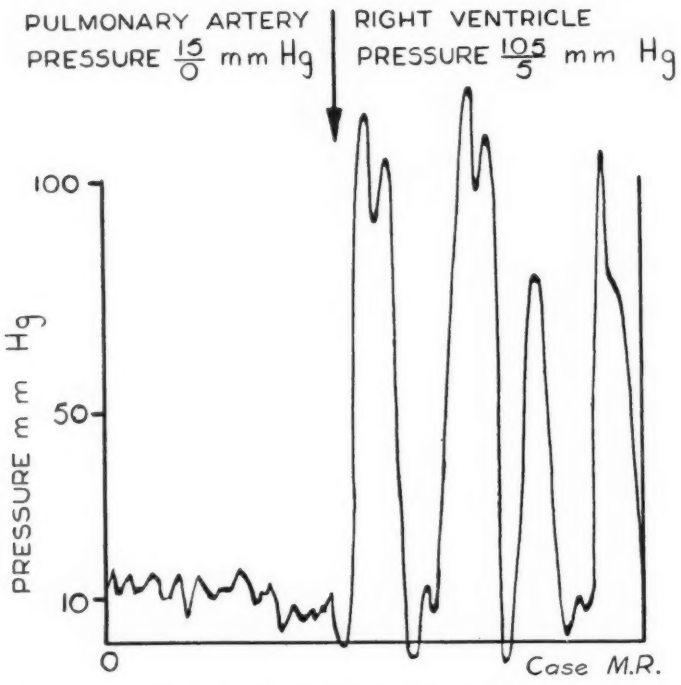

FIG. 6.—Tracing of pulse curve obtained on withdrawing the catheter through a pulmonary stenosis into the right ventricle. Case 3 (0051).

In our own experience, and that of other workers, catheterization directly demonstrates the stenosis in only about one-half of the cases of Fallot's tetralogy. In the other half of the cases it has not been found possible to catheterize the pulmonary artery, seldom because the stenosed ostium is too narrow but, as judged by the position of the catheter on the X-ray screen, because its tip is caught up by the muscle ridge surrounding an infundibular stenosis, or by the hypertrophied papillary muscles. In such cases the finding of a high pressure in the ventricle is not sufficient evidence on which to base a diagnosis of pulmonary stenosis, for this may occur in the absence of obstruction to the pulmonary orifice as, for example, in such conditions as patency of the ventricular septum, Eisenmenger's syndrome, or transposition of the great vessels. Estimation of the pulmonary blood flow, using the right ventricular sample of blood, may show whether the pulmonary blood flow is materially reduced. We have pointed out, however, that for various reasons this calculation is only approximate.

In a few cases dextroposition of the aorta can be demonstrated by passing the catheter through into it from the right ventricle (Fig. 8). Usually, however, the catheter passes into the pulmonary artery. The venoarterial shunt, resulting from the dextroposition, is shown by the lowered oxygen

saturation of the arterial blood. An approximate estimation of the volume of the shunt can be made by subtracting the pulmonary from the systemic blood flow.

For the selection of cases for operation, Taussig (1948) stresses the importance of showing a reduced pulmonary blood flow. From our own experience, however, the demonstration of a lowered arterial oxygen is of equal importance because the lower the saturation of the arterial blood the more useful will be its circulation through the lungs. For example, in a case of pulmonary stenosis with a very small septal defect, such as Case 6, with an arterial saturation of 91 per cent and a much reduced systemic blood flow, recirculation of the already arterialized blood through the lungs could improve the saturation but little. Moreover, it might be harmful to reduce further the systemic blood flow by diverting blood through the lungs.

Examples of the findings at catheterization in four cases of Fallot's tetralogy are given in the appendix (Cases 1, 2, 3, and 4).

Eisenmenger's Complex

Eisenmenger's complex consists of a high ventricular septal defect with an aorta that overrides the right ventricle, and a pulmonary artery that may be dilated. Though much less common, this condition is important because it may be confused clinically with Fallot's tetralogy. It differs from this, however, in that there is no pulmonary stenosis and little or no reduction in blood flow to the lungs. The operation of systemic-pulmonary anastomosis is therefore unlikely to help the patient.

Catheterization clearly excludes pulmonary stenosis by showing equal systolic pressures in right ventricle and pulmonary artery (Fig. 7). There should be no gross reduction in the pulmonary blood supply.

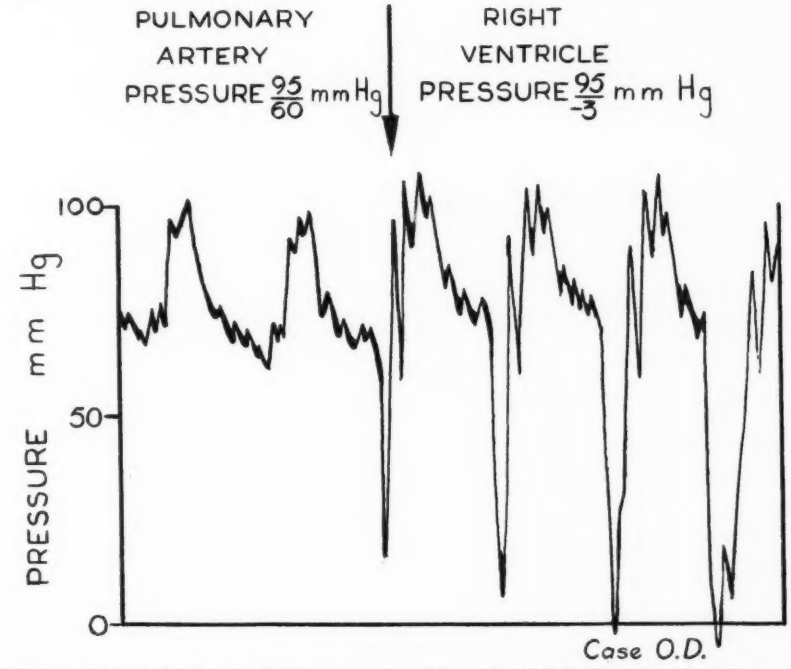

FIG. 7.—Pulse curve obtained in a case of Eisenmenger's syndrome on withdrawing the catheter from the pulmonary artery into the right ventricle. Case 9 (O261).

In Case 3 (see appendix) it was difficult on clinical grounds to know if the increased pulmonary shadows indicated Eisenmenger's complex or an increased collateral circulation. Cardiac catheterization, however, showed a pulmonary stenosis. The calculated pulmonary blood flow was 2·6, and the systemic blood flow 4·3 litres per square metre a minute. The reduction in pulmonary blood flow was therefore small, though there was no doubt about the pulmonary stenosis.

Eisenmenger's complex is generally regarded as a malformation distinct from transposition of the great vessels. There is evidence, however, to show that the effect upon the circulation is the same in the two conditions. In one (Case 9) of our cases of Eisenmenger's complex we were able to pass the catheter into the pulmonary artery. The oxygen content of the blood sample withdrawn from it was higher (25·6 volumes per cent) than that from the right ventricle (21·6 volumes per cent), thus showing that the pulmonary artery received blood from both ventricles. The reduced arterial saturation showed that the aorta also received blood from both ventricles. Analysis of the data given by Bing (1947*b*) for four cases of Eisenmenger's complex shows that in three the oxygen content of the pulmonary artery blood was, as in our case, higher than that in the right ventricle and that the arterial oxygen saturation was reduced. Eisenmenger's complex may therefore be regarded as in effect a functional form of transposition of the great vessels.

A point of interest may be noted in passing. Bing (1947) finds that in all four of his cases the diastolic pressure in the pulmonary artery was raised, and this, together with a nearly normal blood flow through the lungs, points to an increased resistance in the pulmonary vascular bed. Fig. 7 shows the high diastolic pressure in the pulmonary artery in our Case 9. In this instance the calculated pulmonary blood flow was 2·1 litres per square metre a minute. The cause of this increased resistance is not known, though Bing seems to suggest that it is due to an endarteritic change in the pulmonary arterioles. In other conditions, however, in which the pulmonary vascular bed is subjected to a high blood pressure (transposition of great vessels and widely patent ductus arteriosus) the pulmonary blood flow is often increased and not reduced.

Transposition of the Great Vessels

Catheterization is of great value in establishing the diagnosis of transposition of the great vessels since only by this means can it be shown that the blood in the pulmonary artery is of higher oxygen content than blood in the aorta. Also, an estimation can be made of the relative amounts of right ventricular and left ventricular blood entering the two great vessels. In two of our four suspected cases the catheter passed, from the right ventricle into the aorta but could not be inserted into the pulmonary artery (Fig. 8). In these two cases, therefore, catheterization did not establish the diagnosis of transposition of the great vessels. One of them, thought clinically to be a case of Fallot's tetralogy, later came to necropsy, and transposition with stenosis of the pulmonary artery was revealed (Case P088); in the other transposition of the aorta and pulmonary artery was suspected on clinical grounds and confirmed by angiocardiography (Case O052). In the other two of our four (Cases 10 and 11) the catheter passed from the right ventricle into the pulmonary artery and not into the aorta. Transposition was shown by the finding that the pulmonary artery blood was more oxygenated than that in the systemic arteries. The calculated pulmonary blood flow in both these cases was greater than normal (5·1 and 8·3 litres per square metre a minute) and the pressure in the pulmonary artery increased (88 mm. Hg mean pressure and 80/50 mm. Hg respectively).

Pulmonary Stenosis with Closed Ventricular Septum

This condition has been termed " pure pulmonary stenosis," but for reasons discussed by Allanby and Campbell (1949) the term " pulmonary stenosis with closed ventricular septum " is to be preferred. In most cases there is a defect of the atrial septum through which a venoarterial shunt occurs, though some are entirely without septal defects. There is no difficulty in recognizing the pulmonary stenosis, clinically or by the pressure readings during catheterization of the pulmonary artery, or indirectly by calculation of the pulmonary blood flow. A case with no atrial septal defect,

and therefore no venoarterial shunt, is readily recognized by the normal arterial oxygen saturation (Case 5), even though the greatly reduced cardiac output may be associated with a high degree of peripheral cyanosis (Case 6).

FIG. 8.—Passage of the catheter from the right ventricle into the carotid artery in a case of transposition of the great vessels with right-sided aortic arch. Reference No. O052.

There are patients in whom it is difficult to decide whether the venoarterial shunt occurring with pulmonary stenosis passes through a ventricular septal defect (Fallot's tetralogy) or through a defect of the atrial septum (pulmonary stenosis with closed ventricular septum) or through both. Unfortunately cardiac catheterization often fails to make the differentiation (see Case 8). The defect, generally a patent foramen ovale, is small in these cases and there is no record of it having been recognized by passing the catheter through it into the left atrium. It has also been shown (Fig. 1, 2, and 3) that an atrial septal defect with a venoarterial shunt can very seldom be recognized by the comparison of the oxygen content of atrial and vena caval bloods. Catheterization, there-

fore, in pulmonary stenosis with closed ventricular septum and atrial septal defect is unlikely to demonstrate the atrial septal defect, but the latter may be inferred when the venoarterial shunt is found to be small. Of those cases of the group that have a ventricular septal defect, only one-half may be expected to be diagnosed by the increase in oxygen content on passing from atrium to ventricle (Fig. 4). In the absence of a patent ductus arteriosus the ventricular septal defect may also be shown by the increase in oxygen content on passing from the right ventricle to the pulmonary artery (Fig. 4 and Case 4). The position of the stenosis can be judged on the X-ray screen by the position of the catheter tip when the abrupt increase in pressure occurs between the pulmonary artery and the right ventricle as the catheter is withdrawn. If the change is seen to take place high in the pulmonary conus it is in favour of a valvular or high infundibular stenosis, and if low in the pulmonary conus in favour of a lower infundibular stenosis. Since a valvular stenosis occurs more frequently with a closed ventricular septum, and an infundibular stenosis with a ventricular septal defect the position of the stenosis may provide a further aid to diagnosis.

Whether the septal defect in these cases is atrial or ventricular is, however, not of great surgical importance. The practical point is to decide on the relative volumes of the cardiac output and venoarterial shunt, for the smaller the venoarterial shunt the more is valvulotomy to be preferred to systemic-pulmonary anastomosis.

Atrial Septal Defect

The shunt through an atrial septal defect is always arteriovenous when the lesion is an isolated one or associated with mitral stenosis (Bedford *et al.*, 1941; Brannon *et al.*, 1945; Cournand, 1947). When, however, the atrial septal defect is associated with other cardiac malformations the shunt through it is usually venoarterial. To account for the reversal of the direction of the intra-atrial shunt (as, for example, in pulmonary stenosis with closed ventricular septum) a fall in the left atrial pressure must be inferred, since measurements show no increase in right atrial pressure. Such a reduction in pressure might result from the diminished pulmonary venous return.

An atrial septal defect can sometimes be recognized by passing the catheter through the defect. Even a direct demonstration of a septal defect does not prove that there is normally a shunt as it may be a patent foramen ovale normally covered by a valve; it is still desirable to show by blood oxygen comparisons that a shunt occurs through it. The course of the catheter passing through an atrial septal defect is characteristic (Fig. 9), crossing to the left at a higher level than when going through the tricuspid valve. The catheter tip can sometimes be advanced into a pulmonary vein, the catheter then leaving the heart shadow. Confirmatory evidence is the high oxygen saturation of the blood obtained from the left side of the heart. When the catheter cannot be passed through the atrial septal defect a comparison of the oxygen content of the vena caval and atrial bloods will reveal the presence of the defect if an arteriovenous shunt occurs, but not if the shunt is venoarterial.

With an arteriovenous shunt through an atrial septal defect, the right heart output and pulmonary blood flow are increased, the pulmonary blood flow being as much as 5 times increased (Taylor *et al.*, 1948, Case 6). In such cases, in spite of the large amount of blood passing through the atrial septal defect into the right atrium, the right atrial pressure is rarely raised above normal. Right ventricular and pulmonary artery pressure may be slightly raised but occasionally may be much increased (Dexter, 1947, Case 1, and Taylor *et al.*, 1948, Case 3). The systemic blood flow, calculated from the mean of the oxygen contents of the superior and inferior venæ cavæ, is not reduced.

It should be noted that a number of malformations may also give rise to increased oxygen content of the right atrial blood and so lead to the suspicion of an atrial septal defect. The most frequently encountered (three times in our series) is the opening of an anomalous pulmonary vein directly into the right atrium. Until recently this condition has been recognized only after death (Brody, 1942; Taussig, 1947) but Cournand *et al.* (1949) have described one case diagnosed during life. In Cournand's, as in our three cases, this was shown when the catheter slipped from the atrium into a pulmonary vein of the right lung (Fig. 10). We have verified the location of the tip by

FIG. 9.—Passage of the catheter through an atrial septal defect and into a left pulmonary vein. The catheter passes from the right atrium over to the left side of the heart at a higher level than when passing into the right ventricle. Reference No. P021.

FIG. 10.—Passage of the catheter from the right atrium into a pulmonary vein which opens directly into the atrium. Reference No. P021.

screening in the oblique position and by drawing arterialized blood from the catheter. In two of the three patients an atrial septal defect was also demonstrated. The other and rarer conditions which we have not encountered personally are (1) an arteriovenous fistula between a coronary artery and the coronary sinus, (2) tricuspid insufficiency associated with a ventricular septal defect, (3) pulmonary and tricuspid valve insufficiency in the presence of a patent ductus arteriosus, (4) a congenital communication between the left ventricle and the right atrium (Perry *et al.*, 1949), and (5) a persistent common atrio-ventricular ostium.

Lutembacher's Syndrome

The association of an atrial septal defect with mitral stenosis was first described by Lutembacher (1916). The clinical diagnosis of the condition usually presents no difficulties, but doubt may arise whether mitral stenosis is present in a case of atrial septal defect, or whether an atrial septal defect is present in a case of mitral stenosis.

There is yet insufficient evidence to show how far catheterization can assist in the diagnosis of Lutembacher's syndrome. So far as we are aware no catheterization findings have been reported in this condition. Among Brannon *et al.* (1945) cases of atrial septal defect there is, however, one (Case) described as having a low-pitched rumbling diastolic murmur at the apex of the heart which, though the authors do not refer to it, may be an instance of Lutembacher's syndrome. We ourselves have one example (Case 17) in which mitral stenosis was recognized by the characteristic murmur and clinical evidence of atrial septal defect was also present; on catheterization proof of an atrial septal defect consisted in the passage of the catheter through the defect into the left atrium, and the finding of blood of a high oxygen content in the right atrium. In both these cases right atrial, ventricular, and pulmonary artery pressure were raised well above normal. These findings are to

be expected from the combination of mitral stenosis and atrial septal defect. In our patient the systemic flow, calculated from the mean oxygen content of the superior and inferior vena caval bloods was considerably reduced, but was normal in the case of Brannon *et al.* There is as yet no necropsy confirmation of the condition in either of these.

Whilst the findings obtained in these two cases were to be expected in Lutembacher's syndrome, there is some doubt whether they are diagnostic because some instances of atrial septal defect without a suggestion of mitral stenosis have been reported with markedly raised pressures in the right ventricle and pulmonary artery (Dexter *et al.*, 1947, Case 1, and Taylor *et al.*, 1948, Case 3). This rise of pulmonary arterial pressure is unusual in uncomplicated atrial septal defect, and in the discussion Dexter and Taylor do not consider the possibility of mitral stenosis having been present. Whilst a reduced systemic blood flow would be in favour of mitral stenosis, a normal systemic blood flow would not exclude the condition.

Tricuspid Atresia and Pulmonary Atresia

In tricuspid atresia the blood passes from the right atrium through a septal defect into the left atrium and ventricle, and thence directly or indirectly into the pulmonary artery and aorta. In pulmonary atresia the blood reaches the lungs through either a patent ductus arteriosus or from dilated bronchial vessels arising from the aorta. In both tricuspid and pulmonary atresia there may be a small right ventricle. The two abnormalities are considered together since they resemble each other functionally and in both blood for the pulmonary and systemic circulations is derived from the left ventricle. In a patient with the signs and symptoms of Fallot's tetralogy, an electrocardiogram showing left ventricular preponderance is thought to be diagnostic of tricuspid atresia, and angiocardiograms show the abnormal path of the blood through the heart (Campbell and Hills, 1950). On catheterization, the catheter may be seen not only to pass through the atrial septal defect but also to pass into the left ventricle (Case 13, Fig. 11 and 12). Catheterization cannot, however,

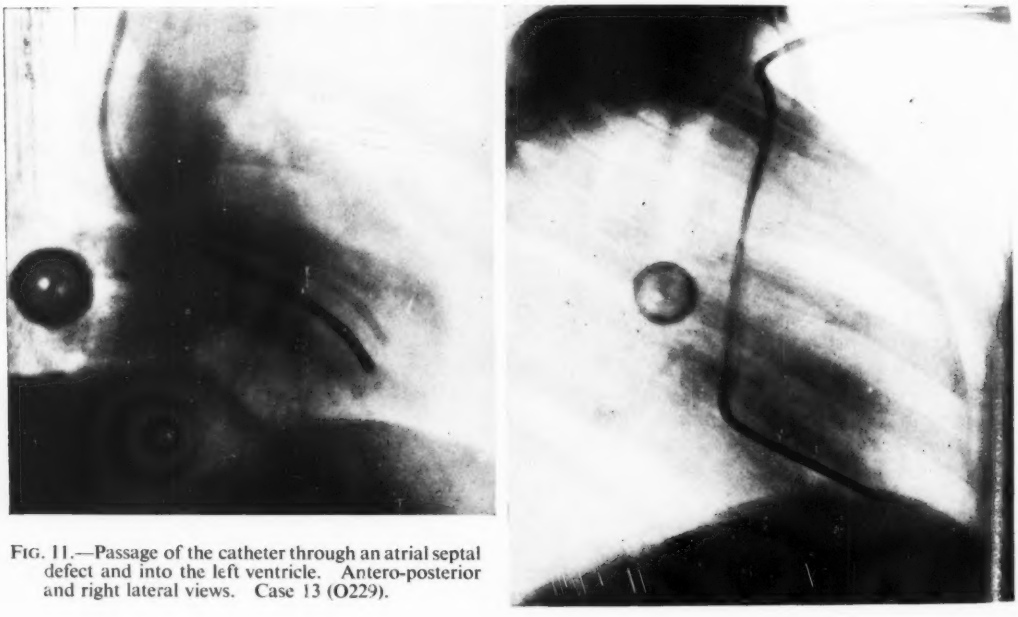

FIG. 11.—Passage of the catheter through an atrial septal defect and into the left ventricle. Antero-posterior and right lateral views. Case 13 (O229).

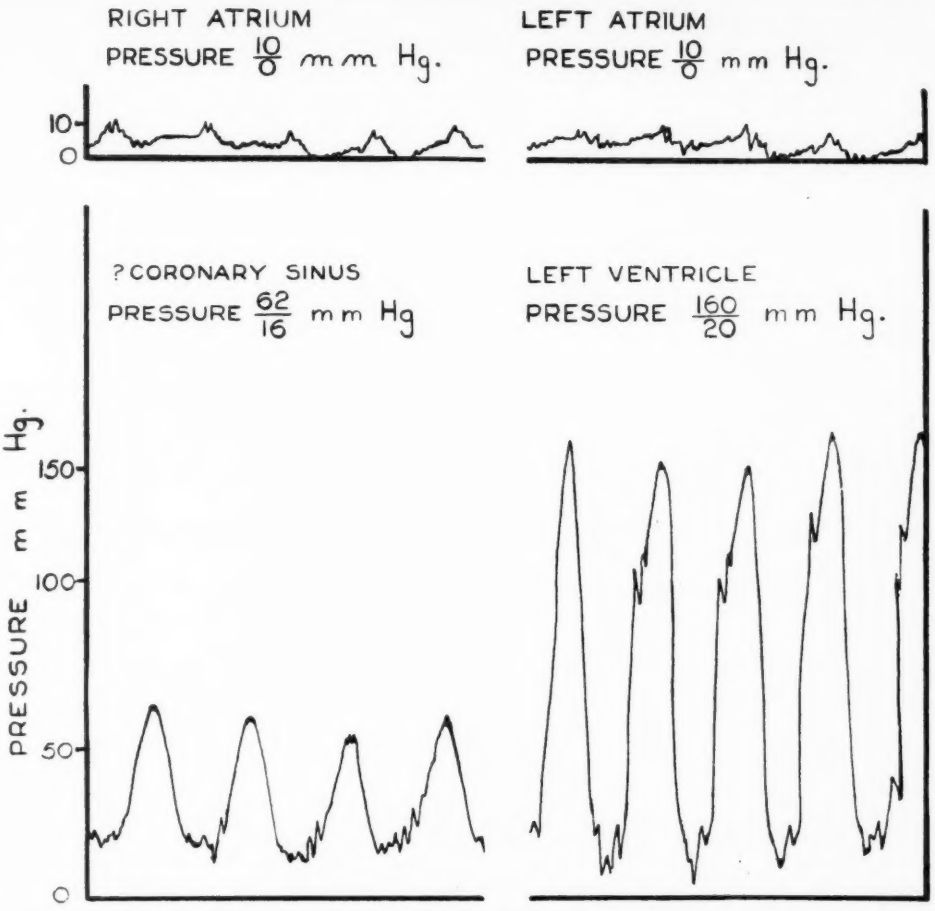

FIG. 12.—Pressure tracings obtained from the right atrium, ? coronary sinus, left atrium, and left ventricle in Case 13 (O229).

distinguish between tricuspid atresia and pulmonary atresia, except in those instances when the catheter is passed from the right atrium into the right ventricle, as, for example, the case reported by Geraci *et al.* (1948).

It is generally assumed that the pulmonary blood flow is reduced, and on this assumption pulmonary systemic anastomosis is carried out with apparent benefit (Potts and Gibson, 1948; Baker *et al.*, 1949; Soulie *et al.*, 1949). The pulmonary blood flow can be calculated if we assume complete mixing of the blood in the left ventricle so that the oxygen content of blood supplied to the lungs can be taken as that of the arterial blood. In 7 of our 9 cases diagnosed on clinical grounds the calculated pulmonary blood flow was decreased (1·2 to 2·5 litres per square metre a minute) but in two slightly increased (3·4 and 3·9 litres per square metre a minute). So far only those of our patients with reduced pulmonary blood flow have been operated on. Operation has been delayed on the two cases with increased blood flow because they have a fairly good exercise tolerance. In most of the accounts given by others data are wanting on which pulmonary blood flow can be

calculated so it is not known whether the successful operations include any in which the pulmonary blood flow was increased. Geraci *et al.* (1948) give the data from two adults, one with tricuspid and the other with pulmonary atresia, from which the pulmonary blood flow can be calculated and shown to be increased. Whether operation was carried out on these two is not recorded, but both are noted to have relatively good exercise tolerances.

That the pulmonary blood flow may be increased or decreased is not unexpected in view of the necropsy findings. In tricuspid atresia the pulmonary artery may arise directly from the left ventricle and if this occurs, as Taussig (1948) points out, increased pulmonary blood flow will be likely. In most cases, however, there is some obstruction to the pulmonary flow.

Truncus Arteriosus and Pulmonary Atresia

Under this heading we are discussing the malformations in which the blood supply to both pulmonary and systemic circulations is derived from a single great vessel which overrides both ventricles. This condition may be either a true truncus arteriosus, or the vessel may be the aorta, in which case an atresic pulmonary artery can be found post-mortem. The diagnosis of these two conditions is difficult to establish by any method and, except at necropsy, the differential diagnosis between them is presumptive. Clinical and X-ray examinations may suggest the condition and angiocardiography and cardiac catheterization may support the diagnosis.

Since the blood supply to the lungs is of the same oxygen content as that of arterial blood it is possible without catheterization to calculate the pulmonary blood flow from the oxygen content of the arterial blood. In three cases where the diagnosis was confirmed (at necropsy in two and at operation in the third), the pulmonary blood flow was thought to be slightly increased in one (3·8 litres) and slightly decreased in the other two (2·5 and 2·0 litres per square metre a minute). The presumed diagnosis of truncus arteriosus in the two catheterized cases has not yet been confirmed. Assuming the diagnosis to be correct, the calculated pulmonary blood flow was normal in one (Case 12); in the other, again assuming the diagnosis, the calculated pulmonary blood flow is about three times the normal. Since the X-ray appearances of the lungs suggest a decreased rather than an increased blood flow, this finding is against the clinical diagnosis.

Patent Ductus Arteriosus

In patent ductus arteriosus, arterial blood flows from the aorta to the pulmonary artery and so an increase in blood oxygen content is found on passing from right ventricle to pulmonary artery. Such an increase in oxygen content may be brought about in several ways (see section on comparison of right ventricular and pulmonary artery bloods) so that confirmatory evidence is required before patent ductus arteriosus can be diagnosed on the grounds of oxygen differences. We have found the characteristic murmur to be the most satisfactory indication of a patent ductus, though proved cases have occurred that do not present this sign.

In most instances of patent ductus arteriosus the pulmonary artery pressure is within normal limits, but in some it is increased. Dexter (1947) found it increased in three of twelve cases. In contrast to Eisenmenger's syndrome (Case 9 and Bing, 1947) in which an increased pulmonary artery pressure was associated with a reduced pulmonary blood flow, the calculated pulmonary blood flow in the three cases was increased (16·9, 14·2, 8·8 litres per square metre a minute). This finding indicates that increased pulmonary artery pressure is not always associated with a marked increase in pulmonary vascular resistance.

Pulmonary Arteriovenous Fistula

The symptoms and some of the signs of pulmonary arteriovenous fistula are so similar to those of congenital heart disease that the condition should be mentioned here. Catheterization does not help in the diagnosis but is useful for assessing the volume of the shunt. From the oxygen saturation of the arterial blood the proportion of the total blood stream passing through the fistulæ can

be calculated, but to calculate the actual blood flows mixed venous blood must be obtained by catheterization (Case 18).

General Remarks

The information that cardiac catheterization can afford in the diagnosis of congenital heart disease has been discussed under the heading of the different malformations. It remains to compare briefly the diagnostic aid to be obtained from cardiac catheterization and angiocardiography, and to state in general terms the value of the former.

Both cardiac catheterization and angiocardiography are proving valuable, the more so because their findings are often complementary. Angiocardiography gives more anatomical, cardiac catheterization more physiological information. Cardiac catheterization gives an indication of the necessity for surgical measures and whether a pulmonary-systemic anastomosis or a valvulotomy operation would be more useful. Angiocardiography is useful, particularly from the surgeons' point of view, in demonstrating the disposition of the great vessels. Angiocardiography is more useful in showing shunts when they are venoarterial whereas cardiac catheterization more surely demonstrates arteriovenous ones. For example, in tricuspid atresia angiocardiography would show the atrial shunt that might escape the cardiac catheter; but in uncomplicated atrial septal defect angiocardiography does not show the shunt as does cardiac catheterization. Angiocardiography does not measure the degree of pulmonary stenosis, and indeed may fail to show minor degrees of the condition; on the other hand, by successful cardiac catheterization pulmonary stenosis can not only be shown but its effects measured, and improvement after surgical treatment can be assessed.

In cases of congenital heart disease presenting no great difficulty in diagnosis, the findings of catheterization can be expected to support the diagnosis. In those instances when difficulties arise in clinical diagnosis, usually when multiple malformations exist, cardiac catheterization may be of great value. If the investigation fails to supply useful information, and this is still a frequent source of disappointment, the reason is either that the catheter cannot be introduced into all the compartments of the heart desirable, or because alternative explanations are possible for the abnormal intracardiac pressures or oxygen contents of the blood samples that have been found. In all but the simplest malformations it is necessary to bring every possible piece of evidence together before making a diagnosis.

Summary

Certain points in the technique of cardiac catheterization are discussed.

In congenital heart disease cardiac catheterization is not without danger. Six of 70 cases developed signs indicative of pulmonary or systemic thrombosis or embolism. One case died.

The difference in oxygen content of blood obtained from the venæ cavæ, right atrium, right ventricle, and pulmonary artery are discussed in relation to the diagnosis of septal defects and patent ductus arteriosus. In the absence of intracardiac shunts and patent ductus arteriosus the oxygen content of right atrial blood should not exceed;

(*a*) that of the superior vena cava by more than 2 volumes per cent * (Fig. 1);
(*b*) that of inferior vena caval blood by more than 3 volumes per cent (Fig. 2);
(*c*) that of the mean of superior and inferior vena caval blood by more than 2 volumes per cent (Fig. 3).

The oxygen content of right ventricular blood should not exceed that of right atrial blood by more than 1 volume per cent (Fig. 4). The oxygen content of pulmonary artery blood should not exceed that of right ventricular blood by more than 0·5 volumes per cent (Fig. 5).

The use of cardiac catheterization in the diagnosis of the following conditions is considered:

* In cases with normal hæmoglobin saturation a difference of oxygen content of 1 volume per cent amounts to 5 per cent difference in oxygen saturation. In polycythæmic cases the same difference of oxygen content represents a smaller difference in oxygen per cent saturation.

Fallot's tetralogy, Eisenmenger's complex, transposition of the great vessels, pulmonary stenosis with closed ventricular septum, tricuspid and pulmonary atresia, truncus arteriosus, atrial and ventricular septal defects, Lutembacher's syndrome, patent ductus arteriosus, and pulmonary hæmangioma.

We are indebted to Dr. Maurice Cambell for his interest in these investigations, and for valuable discussions in the interpretation of clinical and catheterization findings. Our thanks are also due to the Departments of Medical Illustration and Photography for help with the illustrations.

Appendix

Normal Standards for Cardiac Output

Cournand (1945) gives the normal cardiac output for the healthy male adult when estimated by the catheter technique as 3·1 litres a minute per square metre of the body surface. The values for females and children are not known.

Intracardiac Pressures

Bloomfield, Cournand *et al.* (1946) give values for normal intracardiac pressures. Their pressure measurements are referred to the plane of 5 cm. below the angle of Ludwig, and ours to the plane of the skin of the back. It is therefore necessary to add 10 mm. Hg to their figures to make them comparable with ours. If this is done the figures for normal intracardiac pressures become:

Right Atrium	8 to 12 mm. Hg
Right Ventricle	
Systolic	35 to 40 mm. Hg
Diastolic	5 to 15 mm. Hg
Mean	20 mm. Hg
Pulmonary Artery	
Systolic	35 to 40 mm. Hg
Diastolic	15 to 20 mm. Hg
Mean	25 mm. Hg

In our cases the systolic and diastolic pressures were obtained from Hamilton manometer records, and the mean pressure from the aneroid manometer readings.

Notes on the 18 Cases

*Fallot's Tetralogy**

Case 1. The clinical diagnosis of Fallot's tetralogy was supported by the catheterization findings. The oxygen content of the right ventricular blood agreed with that from the right atrium, but the oxygen content of the pulmonary artery blood was distinctly lower. This finding was almost certainly an artefact due to obstruction of the stenosed pulmonary orifice by the catheter for several minutes before the specimen was obtained. Therefore, the oxygen content of the right ventricular blood had to be used in calculating the pulmonary blood flow.

Case 2. The clinical diagnosis of Fallot's tetralogy was supported by the catheterization findings. The increased oxygen content of the right atrial blood as compared with that from the venæ cavæ (see Fig. 1, 2, and 3) suggested the presence of an atrial septal defect, but this was made doubtful by the low oxygen content of the right ventricular blood (see p. 162). The mean of the values of the oxygen content of the vena caval samples was used in the calculation of the systemic blood flow.

Case 3. Clinically there was doubt whether the pulmonary shadows were due to collateral circulation or indicated Eisenmenger's complex. The findings, however, showed pulmonary stenosis to be present, and therefore support the diagnosis of Fallot's tetralogy. The significance of the lowered oxygen content of the pulmonary artery as compared with the right ventricular sample is uncertain. It is probably due to the catheter materially obstructing the lumen of the stenosed artery, though it may also have been due to the restlessness of the child. Because of this the oxygen content of the right ventricular sample was used in the calculation of the pulmonary blood flow. The pulmonary stenosis was of moderate severity and a venoarterial shunt occurred presumably through a ventricular septal defect.

Case 4. The clinical diagnosis was pulmonary stenosis with doubt about the condition of the ventricular septum. Samples were taken from the trunk and from the right and left branches of the pulmonary artery and all showed the same oxygen content which was considerably higher than that obtained on samples from

* All these four cases were greatly improved by subclavian-pulmonary anastemosis or rescetion of the infundibulum (Case 4).

the right ventricle. This finding suggested that either a patent ductus arteriosus or a high ventricular septal defect was present. In the absence of a ductus murmur the latter explanation seemed the more likely one, and at subsequent operation no evidence of a patent ductus arteriosus was found. Evidence of mixing of the blood of the two ventricles in both directions through the ventricular septal defect was given, not only by the increased oxygen content of the pulmonary artery blood, but also by the decreased saturation of the arterial blood. Though the blood flow calculations suggested a slight preponderance of arteriovenous shunt through the defect, the figure for this was well within the limits of experimental error (Dexter *et al.*, 1947). This case appeared to be one of pulmonary stenosis with a small high ventricular septal defect.

Pulmonary Stenosis with Closed Ventricular Septum

Case 5. The clinical diagnosis was pulmonary stenosis. Catheterization results showed that pulmonary stenosis was present but gave no evidence of a septal defect. The mild degree of pulmonary stenosis appeared to be largely compensated for by the increased systolic pressure of the right ventricle so that there was only a slight reduction of the pulmonary flow. The small calculated venoarterial intracardiac shunt was within the limits of experimental error, and in view of the normal arterial oxygen saturation such a shunt was unlikely.

Case 6. In this case of pulmonary stenosis with an intact ventricular septum the right ventricle was only once entered, and though the pressure in it was read no blood sample was obtained. This patient had signs of congestive failure which presumably account for the raised right atrial pressure and the enlargement of this chamber demonstrated by the catheter. The same oxygen saturation was found in samples taken from two different points in the right atrium. The right atrial sample was therefore considered to represent mixed venous blood and used for the calculation of the systemic flow. The low value of the latter, and the almost normal arterial oxygen saturation indicate that the pulmonary blood flow is much reduced and that not more than a minimal septal defect is present. Post-mortem, the pulmonary valves were severely stenosed and a very small opening to a probe was found through the valve covering the foramen ovale.

Case 7. The clinical diagnosis was of severe pulmonary stenosis, and at first angiocardiography failed to show any right to left shunt. The catheterization findings are incomplete because the patient did not stand the procedure well. The extremely low value for the oxygen saturation of the blood from the right pulmonary artery is almost certainly an artefact caused by the prolonged obstruction to the stenosed artery by the catheter, especially as a sample taken from the common pulmonary artery two minutes later showed a still lower oxygen saturation of only 15 per cent. There is no doubt that both pulmonary and systemic blood flows were very low, though accurate figures cannot be given. The lowered arterial oxygen saturation was evidence of a small venoarterial shunt. Post-mortem, severe pulmonary stenosis was found and a slit-like opening (7 by 3 mm.) in the valve covering the foramen ovale.

Case 8. The catheterization findings supported the diagnosis of pulmonary stenosis and showed up a significant venoarterial shunt. The right atrial and right ventricular samples were in good agreement and when compared with them the lowered oxygen saturation of the pulmonary blood sample suggested that the catheter had obstructed the pulmonary artery. This was also suggested by the sense of release from grip which was felt when the catheter was withdrawn from the pulmonary artery. The right ventricular sample was used, therefore, in calculating the pulmonary blood flow. A pulmonary vein draining blood 97 per cent saturated with oxygen into the right atrium was demonstrated: the right atrial sample, therefore, has probably a higher oxygen content than that of true mixed venous blood. The mean oxygen content of the vena caval blood samples would have been more accurate in calculating the systemic blood flows, but unfortunately these had not been taken. The calculated systemic blood flow is therefore likely to be higher than the actual one. This appears to be a case of marked pulmonary stenosis with a moderate venoarterial shunt, and no evidence is obtained as to whether the shunt occurs through the atrial or ventricular septum.

Eisenmenger's Syndrome

Case 9. The clinical diagnosis of Eisenmenger's complex was supported by the catheterization results. There was clear evidence of interventricular mixture of blood, but no preponderance of shunt either to the right or left. The difference in oxygen saturation of the right ventricular and pulmonary artery blood samples suggests a high septal defect and some degree of left to right shunt. Pressure tracings from this case are shown in Fig. 7.

Transposition of the Great Vessels

Case 10. A reliable diagnosis could not be made before catheterization, though transposition with a septal defect was suspected. The finding that the pulmonary artery blood was 82 per cent saturated whilst that of the systemic artery was only 72 per cent made it clear that this was a case of transposition of the great vessels. The figure for the pulmonary artery blood oxygen saturation was duplicated in samples from both the common trunk and the right branch of the pulmonary artery, and the figure for the arterial oxygen saturation was confirmed (68%) by a second arterial sample collected 5 hours after the catheterization.

FINDINGS IN 18 ILLUSTRATIVE CASES

Case No.	Reference number, initials	Sex, age	Surface area, sq. metres (1)	O_2 consumption ml./min./ sq. metre. B.M.R. % of normal (2)	Pressures (mm. Hg.) from skin of back (3)			
					Right atrium	Right ventricle	Pulmonary artery	Systemic artery
	Fallot's Tetralogy							
1.	O105 K. C.	F 15	1·59	132 +6%	10	62	10	128/90
2.	H120 G. S.	F 11	1·01	163 +6%	10	40	10	110/60
3.	O051 M. R.	F 8	0·82	194 +20%	4/−2	105/−5	15/0	80/55
4.	CB11 A. A.	F 20	1·70	115 −6%	12	37	16	108/70
	Pulmonary Stenosis with closed Ventricular Septum							
5.	P206 J. F.	M 16	1·54	132 −14%	10/0	140/21	40/21	130/80
6.	P031 M. C.	F 22	1·53	120 −5%	24	70	—	115/85
7.	H117 D. S.	F 30	1·53	118 −8%	—	100+	16	—
8.	O207 D. W.	F 26	1·48	137 +10%	11	85	11	120/75
	Eisenmenger's Complex							
9.	O261 O. D.	F 23	1·42	152 +20%	0	95/−5	95/55	130/80
	Transposition of Great Vessels							
10.	O076 E. T.	M 14	1·09	169 +6%	10	47	88	100/70
11.	OA06 K. M.	M 7	0·82	182 +3%	8	65/10	80/50	85/?
	Truncus Arteriosus							
12.	P098 H. W.	F 12	0·96	230 +54%	4/−8	117/7	—	120/78 Hamilton manometer
	Pulmonary and/or Tricuspid Atresia							
13.	O229 C. L.	F 6	0·69	222 +30%	4	—	—	160/20 (left ventricle)
14.	O021 V. F.	F 14	1·12	178 +25%	14	—	—	100/55
15.	P057 S. H.	M 19	1·32	168 +19%	11	—	—	95/60
	Patent Ductus Arteriosus							
16.	O280 L. S.	M 27	1·70	138 0	9	14	18	130/55
	Atrial Septal Defect (Lutembacher's Syndrome)							
17.	C227 J. M.	M 25	1·53	167 +12%	20	62	72	105/75
	Pulmonary Hæmangioma							
18.	D. C.	M 27	1·57	147 +7%	8	17	15	105/80

(1) From Du Bois formula.
(2) Percentage of normal calculated on Boothby and Sandiford's (1929) figures.

OF CONGENITAL HEART DISEASE

Oxygen content (volumes %) Percentage saturation							Blood flow litres/min./sq. metre		
Inferior vena cava	Superior vena cava	Right atrium	Right ventricle	Pulmonary artery	Artery	Total capacity	Pulmonary	Systemic	Shunt (4)
16·9	15·7	16·2	16·2	14·1	18·5	30·2	1·0	6·0	5·0
56%	52%	54%	54%	47%	62%	—			
20·5	18·5	23·0	20·7	20·5	24·5	34·1	1·4	3·2	1·8
60%	54%	68%	61%	60%	72%	—			
11·3	13·5	12·2	12·4	11·0	16·7	20·9	2·6	4·3	1·7
54%	65%	58%	59%	53%	80%	—			
—	14·2	13·9	14·7	16·4	21·1	23·8	1·9	1·7	−0·2
—	60%	59%	62%	69%	89%	—			
12·5	10·2	10·9	10·3	10·3	15·4	16·1	2·6	3·0	0·4
78%	63%	68%	64%	64%	96%	—			
—	—	9·0	—	—	22·0	24·3	Very small	0·85	Very small
—	—	37%	—	—	91%	—			
—	—	—	—	9·8	26·4	34·5	Very small	Very small	Small
—	—	—	—	29%	77%	—			
—	—	12·9	13·5	6·3	19·8	28·6	1·0	2·0	1·0
—	—	45%	47%	22%	69%	—			
18·8	22·5	19·8	21·6	25·6	26·8	34·7	2·1	2·2	—
54%	64%	57%	62%	74%	77%	—			
—	15·8	14·0	19·6	21·5	18·8	26·1	5·1	3·5	−1·6
—	61%	54%	75%	82%	72%	—			
15·6	14·5	15·4	20·2	20·8	16·9	24·2	8·3	12·1	3·8
65%	60%	64%	84%	86%	70%	—			
—	—	13·2	14·1	—	13·1	21·8	Not reduced	—	—
—	—	61%	65%	—	60%	—			
				(Left atrium)	(Left ventricle)				
7·8	10·8?	6·4	6	9·6	11·4	31·4	—	—	—
25%	34%?	20%	2%	30%	36%	—			
19·6	—	18·6	—	—	25·6	31·6	4·4	app. 2·5	−1·9
62%	—	59%	—	—	81%	—			
17·4	19·2	16·5	—	—	21·7	29·8	>1·4<3·5	3·2	veno-arterial
59%	65%	56%	—	—	73%	—			
—	—	12·9	14·0	15·5	18·5	20·2	3·7	2·4	−1·3
—	—	64%	70%	77%	92%	—			
—	12·1	12·2/15·7	15·6/17·3	16·2	21·5	23·5	2·7	1·8	−0·9
—	52%	52%/67%	67%/74%	69%	92%	—			
23·6	21·1	21·0	20·6	21·2	23·1	31·6	1·7 (alveoli)	7·0	5·3 (hæmangioma)
75%	66%	66%	65%	67%	73%	—			

(3) A single number indicates mean pressure (aneroid manometer); two numbers indicate systolic and diastolic pressure.

(4) A negative sign indicates an arteriovenous shunt, otherwise the shunts are venoarterial.

This transposition may have been more functional than anatomical because though the catheter could be passed easily through into the pulmonary artery it could not be passed into the aorta. Mean blood pressures only were obtained, but it was likely that systolic pressures in the right ventricle, pulmonary artery, and aorta were equal. Further evidence of considerable interventricular mixing of blood was given by the higher oxygen content of the right ventricle as compared with the superior vena cava and right atrial samples. The pulmonary blood flow was greatly increased. It was concluded that a large ventricular septal defect with transpositions of the great vessels was present.

Case 11. The clinical diagnosis lay between transposition with a septal defect and Eisenmenger's complex. The catheterization was done under avertin and pentothal anæsthesia. The results showed interventricular mixing of blood by the increase in oxygen content in passing from the right atrium to ventricle, and demonstrated the transposition by the fact that the oxygen saturation of the arterial blood was markedly lower than that obtained from the pulmonary artery. For some reason unknown the systolic pressure in the pulmonary artery appeared to be higher than that in the right ventricle. The calculated blood flows were greatly increased. The final diagnosis was of transposition of the great vessels with a ventricular septal defect.

Truncus Arteriosus

Case 12. The clinical diagnosis of a truncus arteriosus was supported by the results of catheterization. A pulmonary vein draining blood (97% saturated) into the right atrium was demonstrated, and also an atrial septal defect. The catheter passed into what appeared to be a vessel of wide diameter (? truncus) and on into a right-sided aortic arch. No pulmonary branches were demonstrated. The blood samples were of limited value because the child was anxious and cried at times, but they indicated that complete mixing of systemic and pulmonary venous bloods had occurred in the common atrium. The systemic blood flow cannot be computed because no sample of mixed venous blood was obtainable as the child finally ceased to co-operate before vena caval samples could be obtained. Assuming that the pulmonary vessels are derived from a truncus arteriosus, the pulmonary blood flow can be calculated as 3 litres a minute per square metre of body surface. The conclusions to be drawn from the investigation are that an atrial septal defect was present, and that an anomalous pulmonary vein drained into the right atrium; there was evidence in favour of a common arterial trunk and the presence of two ventricles, but the existence of a pulmonary artery cannot be ruled out.

Tricuspid Atresia and Pulmonary Atresia

Case 13. The clinical diagnosis in this case was tricuspid atresia. The child was catheterized under only local anæsthesia and remained co-operative throughout. From the right atrium the catheter entered what was at first thought to be a small right ventricle, as judged by the position of the catheter and the pressure measured. The sample of blood obtained from it, however, was only 2 per cent saturated and it seems more likely that the structure entered was the coronary sinus, which the catheter had obstructed. The catheter was withdrawn and the left atrium entered through a large atrial septal defect; from there the tip was advanced into the left ventricle (Fig. 11). For fear of injuring the endocardium the catheter was not further manipulated in the ventricle and the aorta was not entered. As all blood samples, especially the one obtained from the right ventricle, were of such low oxygen content calculation of blood flows does not appear to be justified. The conclusions drawn were that the child had an atrial septal defect through which a venoarterial shunt occurred. The pressure tracings are shown in Fig. 12.

At the end of the catheterization the child complained of nausea and vomited twice, following which she passed into coma. Respirations stopped about two minutes later when a feeble pulse could still be felt. She improved with artificial respiration and oxygen and regained consciousness about 10 minutes later. One month later she had an angiocardiogram, and a few weeks later she suddenly collapsed in bed and died. The post-mortem findings were a large atrial septal defect producing what was practically a common atrium, a small right ventricle with hypertrophied walls, narrowed tricuspid valve, and shortened chordæ tendineæ. There was a slit-like opening high in the ventricular septum and several small ones in the lower part of the septum. The aorta arose entirely from the right ventricle, from which also arose a hypoplastic pulmonary artery with under-developed but well separated cusps. A high degree of pulmonary subvalvular stenosis was present, narrowing the lumen to a little over 1 mm. in diameter. The blood supply to the lungs arose from well developed anterior and superior bronchial arteries. This case was therefore strictly neither an example of tricuspid or of pulmonary atresia, but of complete transposition of the aorta and marked pulmonary stenosis. The case is being reported fully in the Guy's Hospital Reports.

Case 14. This girl was diagnosed clinically as a case of Fallot's tetralogy with a large compensating ductus arteriosus. She was twice catheterized but on neither occasion could an exit be found from the right atrium. Post-mortem, there was a large patent foramen ovale and atresia of the pulmonary orifice and a small right ventricle. There was a well developed pulmonary artery which was supplied from the aorta via a large patent ductus arteriosus. With the knowledge of the post-mortem findings the blood flows shown in the table were calculated.

Case 15. The clinical diagnosis was tricuspid atresia. At catheterization no exit could be found from the right atrium into either the right ventricle or the left atrium. In the absence of a sure anatomical diagnosis two figures were calculated for the pulmonary blood flow, the larger assuming that the pulmonary blood supply was derived entirely from the arterial blood, and the smaller assuming that the pulmonary blood supply was derived from such mixed venous blood as was sampled in the right atrium. In either case it appears that the pulmonary blood flow was reduced.

Patent Ductus Arteriosus

Case 16. The obvious clinical diagnosis of patent ductus arteriosus was confirmed by the finding that there was a significantly higher oxygen content of the blood in both branches of the pulmonary artery than that in the right ventricle. It will be noticed that the oxygen content of the right ventricular blood is somewhat higher than that of the right atrial blood. This may be due to the right atrial sample not being a representative one, it may be questionable evidence of a ventricular septal defect, or perhaps evidence of regurgitation through the pulmonary valves; had vena caval samples been taken the answer to the first of these possibilities would have been available.

Atrial Septal Defect and Mitral Stenosis (Lutembacher's Syndrome)

Case 17. The catheterization findings confirmed the clinical diagnosis of atrial septal defect. The right atrial pressure was raised, as was also the mean right ventricular and pulmonary artery pressures. The samples of blood of various oxygen content obtained from the right atrium and ventricle gave evidence of incomplete mixing of blood therein. The slightly lowered oxygen saturation of the arterial blood suggests that there may be some admixture of venous blood from the right to the left atrium even though the overall shunt is arteriovenous. The systemic blood flow is significantly reduced and the pulmonary blood flow is a low normal value. These findings suggest that mitral stenosis is also present, making this case an example of Lutembacher's syndrome.

Pulmonary Hæmangioma

Case 18. This case was diagnosed clinically. It was thought that catheterization had diagnosed an angioma of the liver, for it was found that the oxygen content of the inferior vena caval blood was the same as that of the arterial blood. In cases of cyanotic heart disease, however, it is not very unusual to find that the oxygen content of inferior vena caval blood is nearly that of the arterial blood, but it is unusual to find them the same. Since he was known to have arteriovenous fistulæ in lips and buttocks it was thought that the inferior vena caval specimen derived from the effluent of an angioma of the liver. The cardiac output was greatly increased and it can be calculated that about 75 per cent of the right ventricular output passed through the angioma rather than through the alveolar capillaries. The diagnosis was confirmed post mortem, but the diagnosis of the hepatic angioma proved to be incorrect, though dilated sinuses suggested that a large proportion of the increased systemic circulation was passing through the liver. This case is fully described by Baker and Trounce (1949).

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RADIOLOGICAL FEATURES OF ENLARGED BRONCHIAL ARTERIES

BY

MAURICE CAMPBELL AND FRANCES GARDNER

From the Cardiac Departments of Guy's Hospital and the Royal Free Hospital

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Changes in the radiological appearances of the hilar region of the lungs may indicate that the pulmonary blood supply is not normal. In atresia of the pulmonary valve, the pulmonary arteries may be absent, but more often they are small and may be supplied or supplemented by anomalous vessels. Then blood reaches the lungs mainly by the bronchial arteries or by other collaterals and there is little flow through the diminutive pulmonary arteries.

We wish to describe certain features of the X-ray films—both with intravenous injection of opaque substances and without this help—features that indicate an abnormal blood supply to the lungs by enlarged bronchial and collateral arteries. After a short account of present knowledge of the subject we shall discuss some teleradiograms with these unusual appearances. We shall then describe the angiocardiograms of some cases which we believe show that these collateral vessels are largely responsible for the abnormal vascular pattern.

We shall first consider two patients with anomalous pulmonary blood supply, one with a clinical diagnosis of truncus arteriosus and the other with pulmonary atresia or possibly truncus arteriosus where the diagnosis was supported by direct observation at operation. We shall then describe five other patients in whom the presence of hypertrophied bronchial arteries and pulmonary atresia was confirmed post-mortem.

Present Views

Pulmonary atresia and common arterial trunk are the two conditions in which bronchial arteries are likely to be seen.

Hypertrophy of these arteries as part of the collateral circulation has been known for a long time and was referred to by Chevers (1846) and Peacock (1858). Abbott (1932) describes the bronchial, mediastinal, and œsophageal arteries as an important source of collateral blood supply to the lungs in pulmonary atresia, and also the anomalous arteries arising from the subclavian, the thyroidea ima, and the aorta itself; and Brown (1939) refers to their occurrence in pulmonary atresia and occasionally in transposition. But except for their pathological anatomy little was known until recently. Danelius (1942) emphasized the absence of a hilar comma in a case of truncus arteriosus and looking at the X-ray afterwards thought it should have been possible to suspect the diagnosis before death.

Taussig (1947) points out that this absence of the hilar comma is seen also with pulmonary atresia. She discusses the importance of the bronchial arteries, particularly in cases of truncus arteriosus, and states that when they are much enlarged, providing the main circulation to the lungs, they may cause the aortic arch to be fuzzy and indistinct. This can be seen in her Fig. 79, 83, and 88, and in the original illustration of Danelius (1942). The bronchial arteries may also indent the œsophagus or cause it to deviate from its normal course, and more emphasis is placed on this as evidence of their enlargement than on changes in the aortic outline.

Taussig thinks that when the circulation to the lungs is by way of bronchial or anomalous vessels

the lungs are remarkably clear, but that in contrast, when the posterior mediastinal vessels are greatly enlarged, the hilar shadows are exaggerated. She thinks that pulmonary atresia rarely leads to much development of the bronchial arteries because the ductus arteriosus, being patent in fœtal life, discourages their hypertrophy at this early stage: but this is not borne out by our cases.

Radiological Appearances

In normal teleradiograms the descending branches of the right and left pulmonary arteries are seen as gently curved structures, concave towards the mid-line and running downwards and slightly outwards from the lung hila. They are well known to everyone though relatively little has been written about them except in the recent papers of Appleton (1944) and Lodge (1946). On the right this branch of the pulmonary artery often lies entirely outside the heart shadow. Its lateral margin may, however, coincide with or lie entirely within the right auricular contour and in these circumstances it can only be recognized in the more penetrating films. On the left, the upper part of the descending pulmonary artery frequently contributes to the middle cardiac segment but the lower part generally lies entirely behind the heart shadow.

In patients with the tetralogy of Fallot the normal anatomy of the pulmonary arteries can usually be recognized in teleradiograms of the chest. The pulmonary artery shadows may look small, or

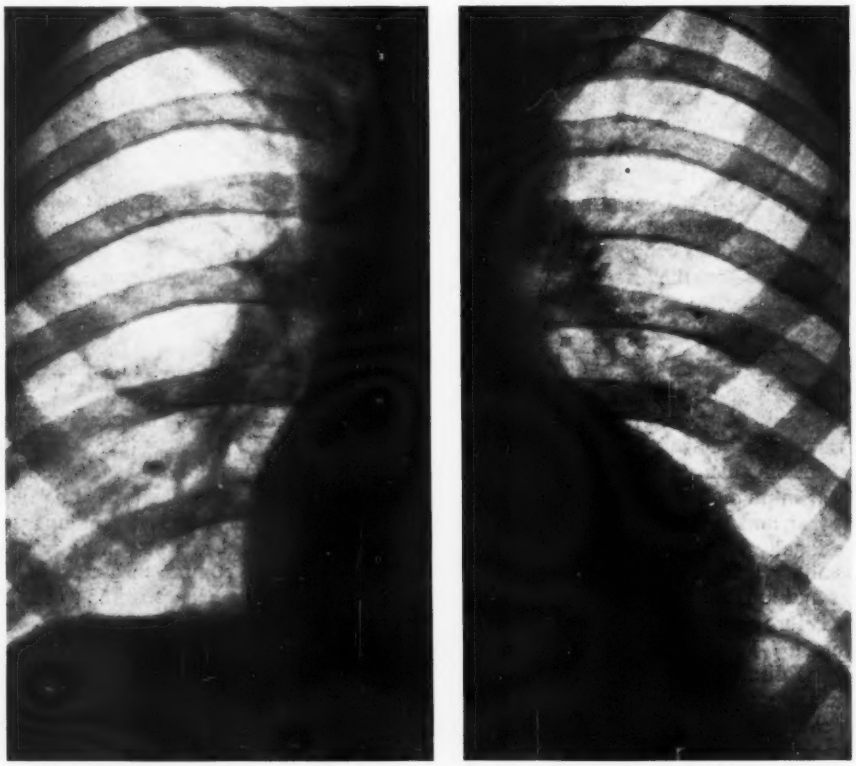
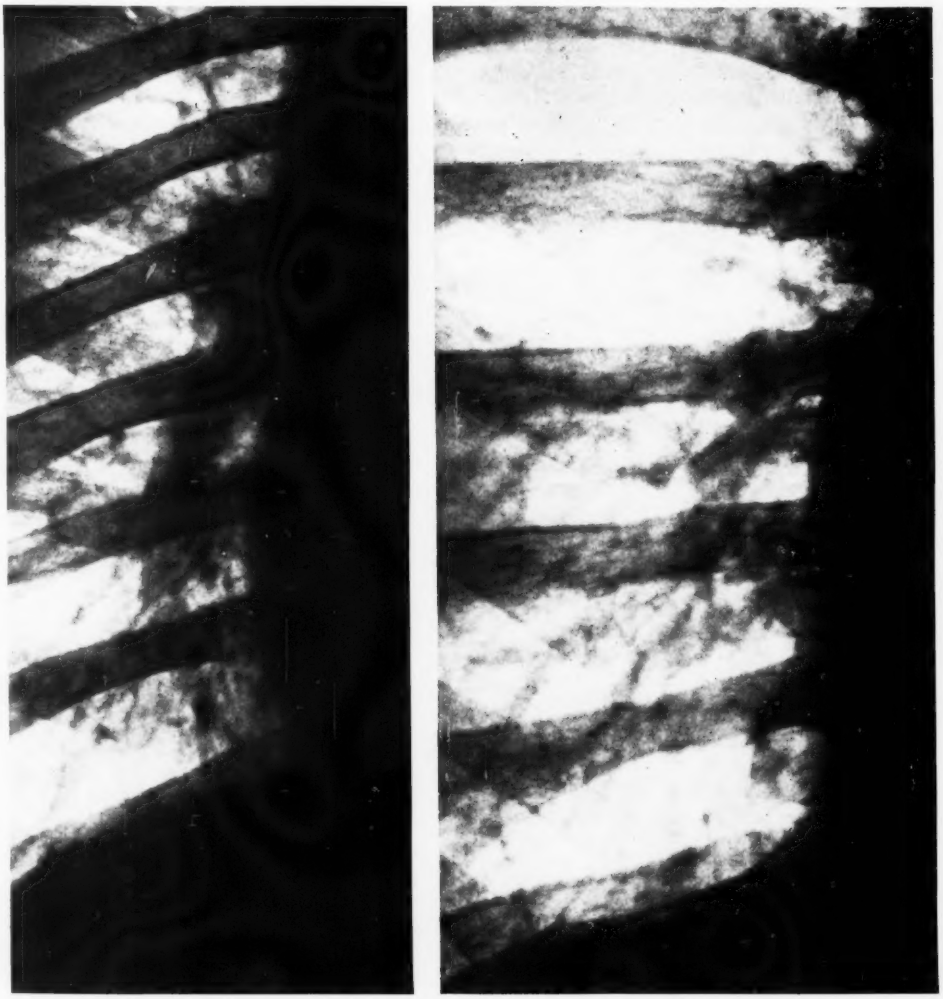


Fig. 1.—Teleradiogram from a patient with Fallot's tetralogy showing right and left pulmonary arteries. Although the arteries are small they have the same general features as normal, and the smooth downward curve can be seen on both sides.

may sometimes be more irregular than normally. Fig. 1 shows the descending branches of both pulmonary arteries: their normal outline is clearly seen, though they are smaller than usual and obviously carry little blood, as the lung fields look unusually light. After a successful subclavian-pulmonary anastomosis the artery became larger and the lung fields denser.

Fig. 2 shows the right hilar region from two other patients with Fallot's tetralogy, the first



A B

FIG. 2.—The right pulmonary artery from two patients with Fallot's tetralogy.

(A) The descending branch of the right pulmonary artery is fairly well seen; there is some branching but rather less than normally and the pattern in the lung fields is not quite usual and suggests some anastomoses. The general density of the lung fields is diminished, especially in the lower part.

(B) The shadow of the descending branch of the right pulmonary artery is less well seen and more irregular, and the branches seem small and somewhat unusual. The density of the lung fields is diminished, especially in the upper part.

showing a small but normal pulmonary artery with light lung fields, and the second showing a fainter and more irregular shadow from a patient where the pulmonary blood flow was greatly diminished.

Absence of these curved vascular shadows and the presence of the abnormal shadows to be described are the radiological features that suggest a bronchial artery blood supply to the lungs because of pulmonary atresia or truncus arteriosus. On the left these abnormal shadows are rounded and nodular and do not seem to connect directly with the outline of the heart; sometimes they are directed outwards and upwards in place of the smooth downward curve of the left pulmonary artery and its descending branch. On the right there may be a rather diffuse mottled mass of collateral vessels, spreading much higher than the normal position of the right pulmonary artery because the bronchial arteries often descend from the under surface of the aortic arch. Both these features were present in most of our patients and even the attenuated hilar comma in Case 5 (Fig. 13) and the co-existence of abnormal anastomoses to the small pulmonary artery in Cases 2, 4, and 6 (Fig. 7, 11, and 14) did not mask the characteristic appearances.

With angiocardiography the bronchial arteries are seen filling later than the aorta. They

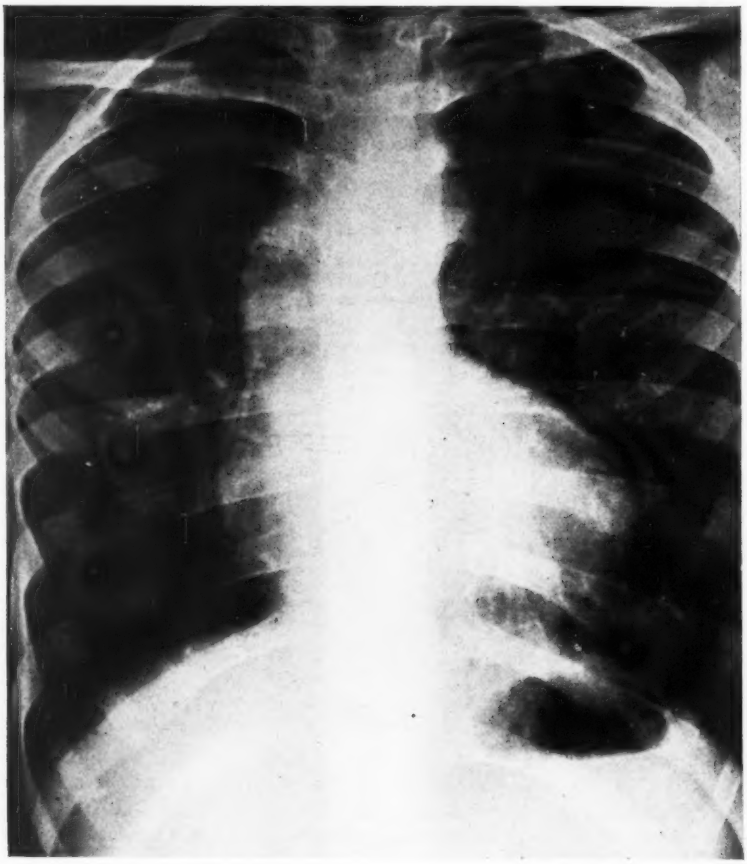


FIG. 3.—Teleradiogram from a child with truncus arteriosus. The normal hilar vascular shadows are absent.

arise from the under surface of the arch or from the descending aorta and fill up to some extent the aortic window before they spread widely around the hilum of the lung. Even with diodone they are difficult to define precisely. The antero-posterior angiocardiograms show that they fill only after the ascending aorta (Fig. 9, 12, and 13) but this may be difficult to demonstrate unless rapid multiple exposures are made. It is in the lateral and left oblique positions (Fig. 4, 10, and 16) that they are most easily recognized. Here the bronchial arteries are seen as dense shadows lying behind the ascending aorta with rather straight branches spread out fanwise in the lung fields.

The first examples (Fig. 3 and 4) are from a cyanotic child, aged 10 years: there was a continuous murmur best heard on the left side behind and the clinical diagnosis was persistent truncus arteriosus

FIG. 4.—Angiocardiogram in the left lateral position from the same child as Fig. 3. At 2 sec. the right auricle and the appendage, the right ventricle, the large common trunk, and the arch are well seen. From the concavity of the arch and from the descending aorta, large tortuous vessels that are hypertrophied bronchial arteries pass to the hilum, and spread out in the lung fields.

with bronchial artery blood supply to the lungs. The teleradiogram (Fig. 3) shows the wide aortic arch and the boot-shaped heart with a deep pulmonary bay. The lung fields are translucent and there are no shadows resembling normal pulmonary arteries. The vascular structures in the lung hila consist of numerous narrow vessels irregularly arranged, and on the left side it is clear that they are not continuous with the cardiac contour.

The angiocardiograms confirm the presence of a common arterial trunk and the absence of pulmonary arteries. In the left lateral position (Fig. 4) dense vascular shadows arising from the concavity of the aortic arch run downwards towards the hila and are distributed in the lung fields. These structures are, we believe, the hypertrophied superior bronchial arteries which, in this instance, are largely responsible for the pulmonary circulation.

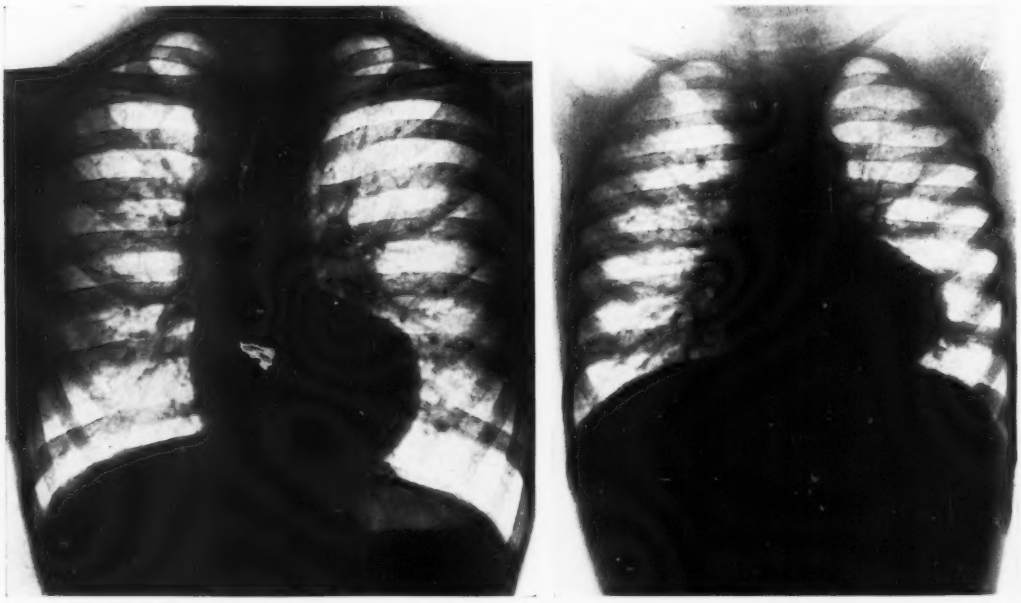


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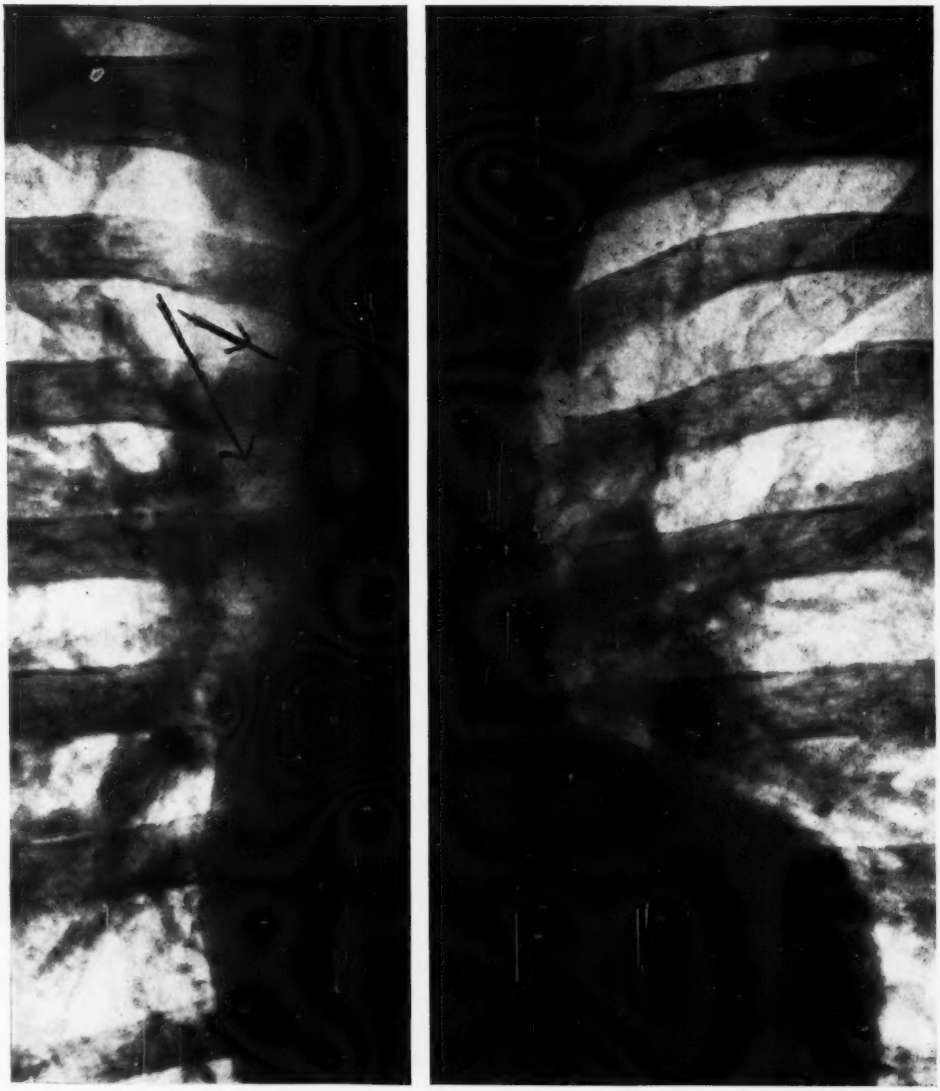
FIG. 5.—Reduced teleradiograms of hypertrophied bronchial arteries in pulmonary atresia.

(A) In the left pulmonary region there are isolated nodular shadows instead of the hilar comma; on the right there is a mottled irregular appearance spreading high up. Case 0087.

(B) Absence of main pulmonary arteries on both sides with numerous smaller bronchial arteries, providing a mottled appearance with rather linear branches. The linear spread is characteristic but otherwise the picture is less typical than Fig. 5A and 6. For detailed description see Fig. 11. Case 4.

Fig. 5 shows the teleradiograms of two further cases and larger pictures of the pertinent parts of the lung fields are shown in Fig. 6 and 11. Fig. 5A and 6 are from a boy, aged 14, with moderate cyanosis and disability from infancy and a continuous murmur in the second left space: the final diagnosis was pulmonary atresia, or possibly truncus arteriosus, with a bronchial artery blood supply to the lungs. The teleradiogram (Fig. 6) is characteristic, with an unusually deep pulmonary bay so that the spine shows through, and with no visible pulmonary arteries. On the left there are two large nodular shadows that do not seem to connect directly with the heart and on angiocardiography fill *after* the aorta. On the right there is a curved shadow (marked with



A B

FIG. 6.—Natural-size view of the right and left hilar regions. The central part of the heart shadow and the outer parts of the lung fields have been cut off to show the pertinent parts on a larger scale. See Fig. 5A.

(A) Absence of the normal right pulmonary artery shadow. At operation no pulmonary artery could be seen, and a vessel (marked with arrows) was seen running down behind the S.V.C. and entering the lung root.

(B) A characteristic picture of the " nodular " appearance when bronchial and other collateral arteries replace the normal left pulmonary artery. Case 0087.

arrows) running downwards behind the superior vena cava and dividing into several branches near the hilum of the lung. The angiocardiograms of this case have already been published (Campbell and Hills, 1950, Fig. 12).

Operation was advised with the hope of finding a vessel that would be adequate for an anastomosis, but none was found. Mr. R. C. Brock's report of his findings was as follows. No pulmonary artery could be found. There seemed to be a single trunk from the aortic arch that gave rise to the right subclavian, common carotid and a third artery, about 1 cm. in diameter, that ran upwards and then downwards behind the superior vena cava and entered the hilum of the right lung. No thrill was felt. The artery, which seemed to have a systemic blood pressure, lay in direct contact with the lower part of the trachea and the right main bronchus.

These two patients are still alive and in good health, but the presence of demonstrable bronchial arteries appears to us to be in no doubt. In the five case reports that follow, the presence of bronchial arteries was suggested by the teleradiograms and confirmed by the comparison of these with the angiocardiograms, and was proved by the post-mortem examination.

Case Reports

These five patients had atresia of the pulmonary valve, though the artery itself was always present, reduced in size and sometimes greatly so. There was always hypertrophy of the right ventricle, a high ventricular septal defect of the same type as that found in Fallot's tetralogy, and an aorta that

Fig. 7.—Radiogram from Case 2, an infant with pulmonary atresia. Massive shadows on the upper right side represent the main area of hypertrophied bronchial arteries and other collaterals. Owing to the enlargement of the heart, the vascular shadows cannot be seen on the left side.

over-rode this defect. Full clinical notes and the pathological anatomy are being described (Allanby, Brinton, Campbell, and Gardner, 1950), so will only be given very shortly here in so far as they are revelant.

Case 2* (Reference No. OA19). S.N., died when four months old and no detailed diagnosis was made. The radiogram shows dense shadows on the right side (Fig. 7) which spread upwards above the normal position of the pulmonary artery.

Post-mortem, there was pulmonary atresia and the right-sided shadows seemed to be due to a large bronchial artery arising from the postero-inferior aspect of the arch of the aorta and passing just below the right main bronchus and behind the right pulmonary artery. Another bronchial artery ran along the upper edge of the right bronchus. A third ran into the hilum of the left lung and anastomosed with the left pulmonary artery.

Even after her death in 1948 we were puzzled by these unusual X-ray appearances in a case where

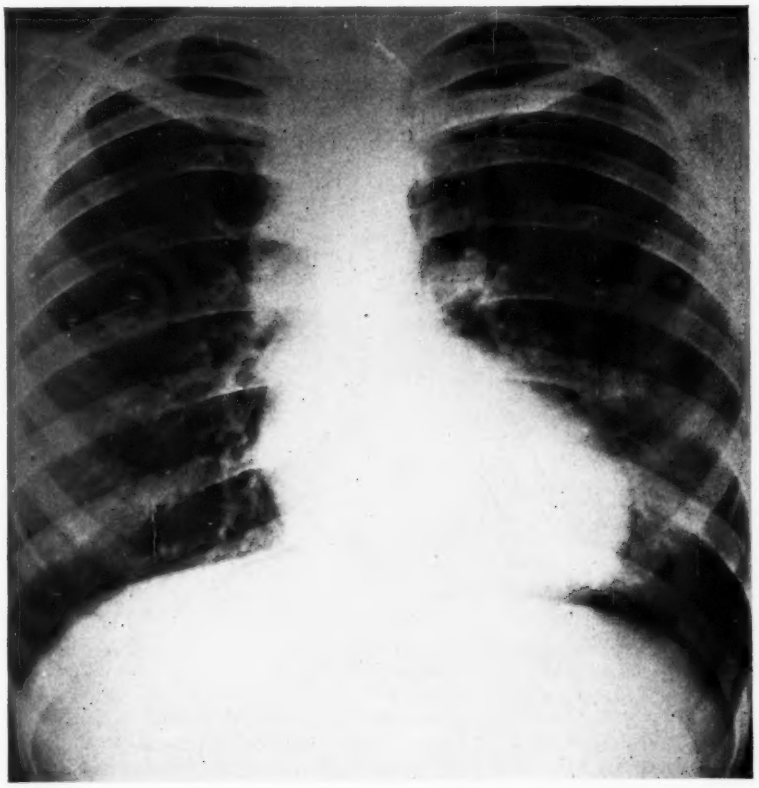


FIG. 8.—Teleradiogram from Case 3, a girl with pulmonary atresia and hypertrophied bronchial arteries. The shadows of the pulmonary arteries are absent. There is a nodular shadow in the left hilum and the vascular pedicle is broadened by abnormal collateral vessels high up on the right.

* Cases 1–6 have been given the same case numbers as in the paper by Allanby *et al.* (1950) to facilitate comparisons. Case 1 had pulmonary atresia with no ventricular septal defect and the circulation was maintained through a patent foramen ovale and a patent ductus arteriosus without enlargement of the bronchial arteries, so is not pertinent to the present discussion.

the blood flow to the lungs was obviously diminished. It is only the experience of the subsequent cases that has revealed the true explanation.

Case 3 (Reference No. O187). S.R., a girl, aged 12, had severe cyanosis and moderately severe disability. The clinical diagnosis was pulmonary atresia and bronchial artery blood supply to the lungs. The teleradiogram (Fig. 8) shows a sabot-shaped heart with a moderate pulmonary bay and a right-sided aortic arch. The hilar vessels are abnormal in configuration—they extend very high on the right side, forming a lateral bulge to the vascular pedicle—and the characteristic comma appearance of the descending branch of the right pulmonary artery is absent. On the left, the vascular shadows have a nodular appearance but separation from the heart shadow is not complete.

In angiocardiograms in the antero-posterior position the aortic arch is filled at two seconds but the hilar vessels are not seen till the third second (Fig. 9). In the left lateral position the right auricle

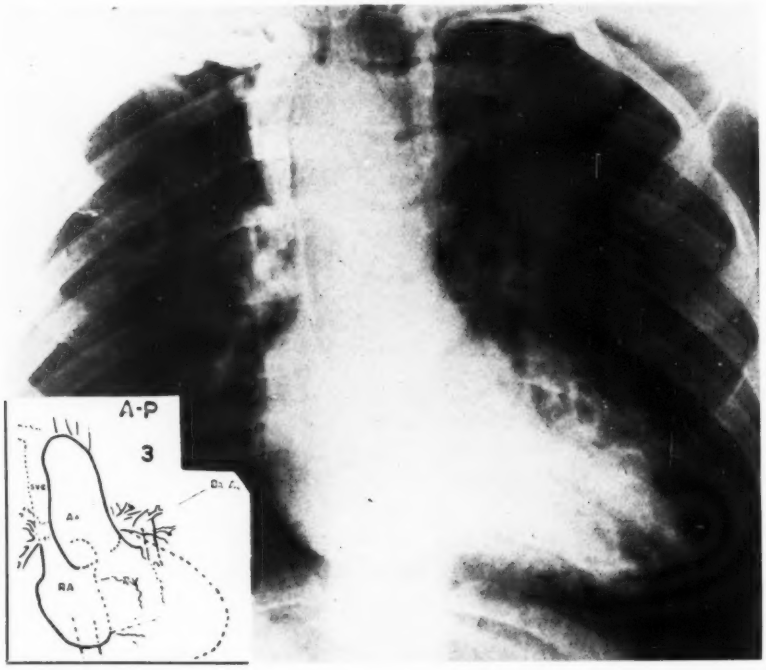


FIG. 9.—Angiocardiogram at 3 sec. in artero-posterior position from Case 3. There is diodone in the ascending and descending aorta and slight filling of the bronchial arteries. There are no visible pulmonary arteries.

and ventricle and the aorta contain diodone at two seconds and ill-defined vascular shadows are seen behind the ascending aorta. In the three-second film (Fig. 10) these abnormal vessels are more obvious; their branches are unusually straight and they spread out fanwise in the lung fields. In no film is there any evidence of the pulmonary artery or its branches.

Post-mortem, the infundibulum was narrowed and there was pulmonary valvular atresia. The pulmonary artery was very narrow, 3 mm. in diameter, but patent beyond the valve. The circulation to the lungs was provided by two large bronchial arteries, arising from the concavity of the aortic arch and running close to the two main bronchi. From the upper part of the descending aorta there were many arteries which formed a free anastomosis round the œsophagus and at the reflection of the pleura before turning into the lungs.

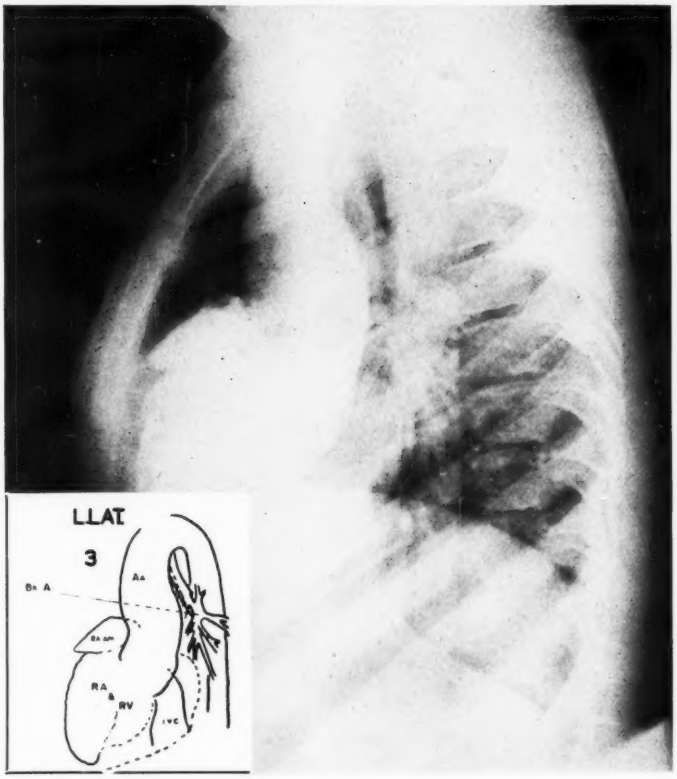


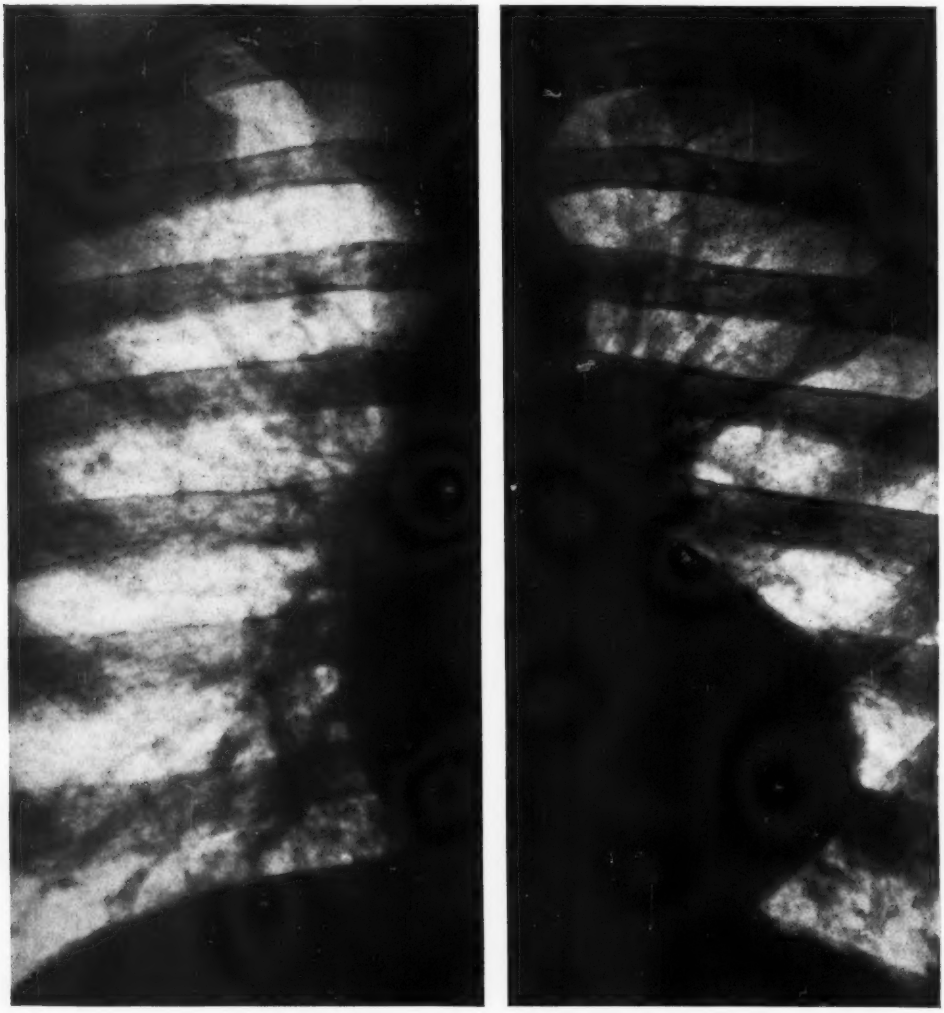
FIG. 10.—Angiocardiogram at 3 sec. in the left lateral position from Case 3. The aorta is filled with diodone and bronchial arteries descend from the concavity of the arch and spread into the lung fields.

Case 4 (Reference No. P048). A.F., a girl, aged 8, was cyanosed and could only walk 50 yards. The teleradiogram is shown in Fig. 5B and 11. On the right side the descending branch of the pulmonary artery is seen but in addition there are narrow straight shadows that do not conform to the normal pattern of pulmonary arterial branching (Lodge, 1946). On the left no pulmonary artery can be seen but there are dense nodular shadows with narrow straight branches spreading into the lung fields.

The angiocardiogram at two seconds shows filling of the large overriding aorta and its branches without any filling of the lungs. By the third second the upper zone of the right lung is filling well in a curious way, and at the bottom of this shadow there is something that might be a small pulmonary artery filling through an anastomosis. By the fourth second this is clearer (Fig. 12) and the lungs are becoming denser and can be seen to be filling on the left as well as on the right. The right lung appears to have a better blood supply than the left and this was confirmed at necropsy.

Post-mortem, there was severe pulmonary valvular stenosis amounting to a functional atresia, as only a fine probe could be passed. The pulmonary trunk was very small with a diameter of 2 mm. but the main branches were almost normal in size. There were three large bronchial arteries (the two larger to the right and the third to the left lung) which received reinforcement from other anastomoses. The upper two accompanied the main bronchi and one anastomosed with the right

pulmonary artery; the lower ran down behind the œsophagus and passed to the lower lobe of the right lung. The total calibre of these must have been much larger than that of the pulmonary artery. There were many small arteries arising from the aorta at the site of the intercostals.



A B

FIG. 11.—Natural-size view of the left and right hilar regions. Absence of pulmonary arteries on both sides. Case 4, see Fig. 5B.

(A) There is general mottling in the hilum and in the lower part some better defined small vessels that appear to cross each other rather than to divide like a normal pulmonary artery. Possibly the shadow above this may represent a small poorly filled pulmonary artery, but above it the shadows are anomalous and resemble collateral vessels.

(B) On the left side there are rounded mottled shadows but less distinct than in Fig. 6, and linear branches spreading upward from them.

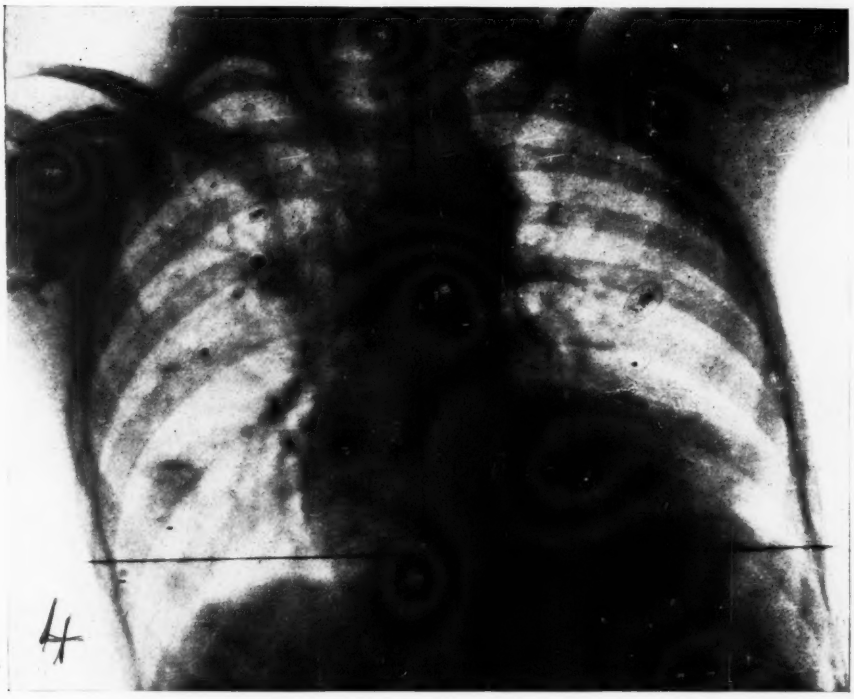


FIG. 12.—Angiocardiogram at 4 sec. from Case 4, a girl with pulmonary atresia. The teleradiogram has been shown in Fig. 5B and 11. In the right hilum there is a broad crescent-shaped shadow, the lower part of which probably represents a small and normally placed pulmonary artery, and the upper part, which seems responsible for the main filling of the lungs, the hypertrophied bronchial arteries. These filled sometime after the aorta. The left side is also beginning to fill in an irregular manner. There was an anastomosis between a bronchial and the right pulmonary artery.

Case 5 (Reference No. O016). J.N., a boy, aged 5, was more like a case of Fallot's tetralogy and pulmonary atresia was not suspected at first. He was the least cyanosed of these patients but could only walk 100 yards. The teleradiogram (Fig. 13A) shows a somewhat diminished blood supply to the lungs and a small pulmonary artery on the right, but no left pulmonary artery could be seen in the pulmonary bay. In the right upper zone there are dense vascular shadows resembling those seen in Case 2.

Angiocardiography shows filling of an overriding aorta at two seconds. At three seconds, and more so at five seconds, the lung fields are becoming opaque but no main pulmonary arteries are seen and the right upper zone shows more density than the rest of the lung. These appearances suggest pulmonary atresia with the lungs filling through dilated bronchial or collateral arteries (Fig. 13B).

Post-mortem, the pulmonary valve was represented by an atresic diaphragm; a dimple, too narrow for any probe, must just have been patent as water could seep through it. The pulmonary artery and its branches were small and the diameter was 6 mm. compared with 13 mm. for the aorta. There was moderate hypertrophy of only one bronchial artery and little of the intercostal arteries so that it seems difficult to understand how the child maintained even his limited activity; probably other collateral vessels were divided on removing the heart.

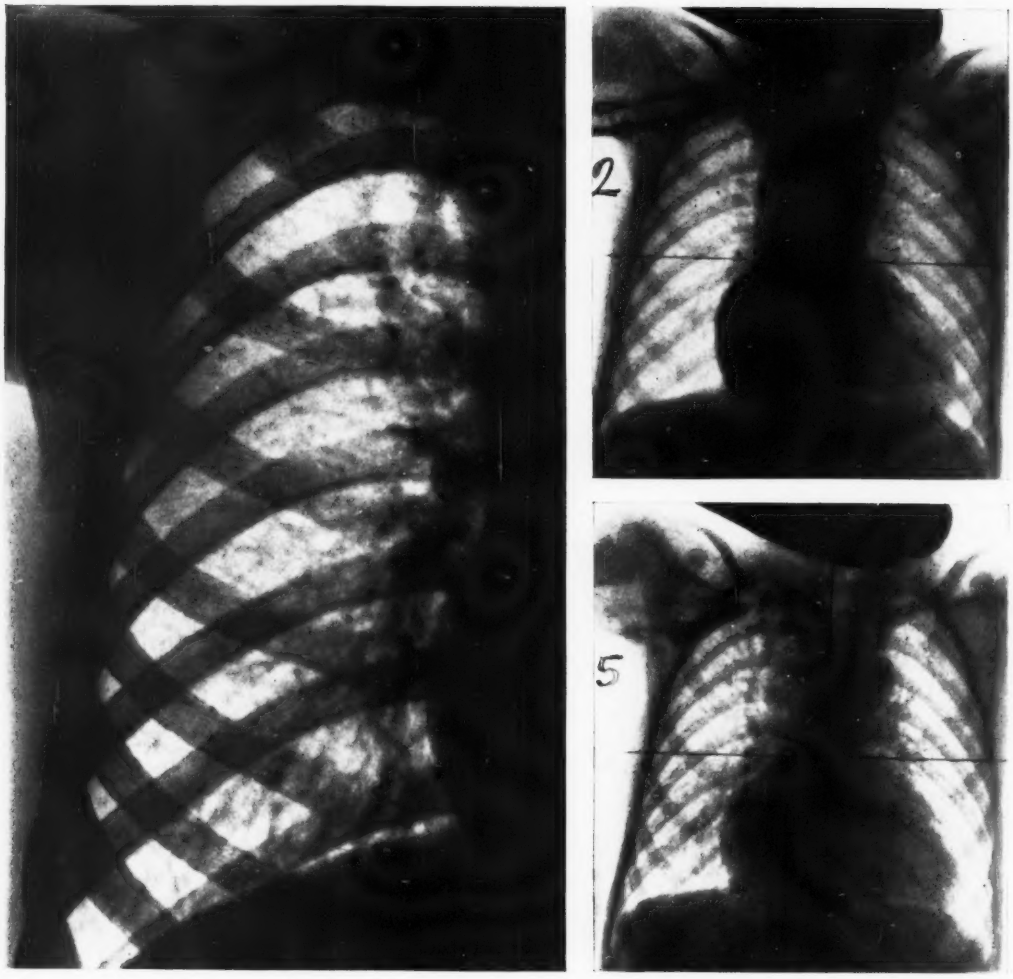


FIG. 13.—From Case 5, a boy with pulmonary atresia.

(A) Teleradiogram of the hilum of the right lung showing the diminutive pulmonary artery, and higher up other anomalous shadows that represent collateral circulation.

(B) Two angiocardiograms from the same patient. The upper at 2 sec. shows an over-riding aorta well outlined and behind the heart the small left pulmonary artery but no filling of the lungs. The lower, at 5 sec., shows the anomalous vessels, especially in the right upper zone, filling from the aorta.

Case 6. J.E., a girl, aged 7, was cyanosed and could only walk about a quarter of a mile slowly. She had a continuous murmur over the left upper chest. The clinical diagnosis was extreme pulmonary stenosis or atresia and persistent patency of the ductus arteriosus. The teleradiogram (Fig. 14) shows a sabot-shaped heart with a fairly deep pulmonary bay. The pulmonary vascular markings are abnormal: on the right the descending branch of the small pulmonary artery is seen

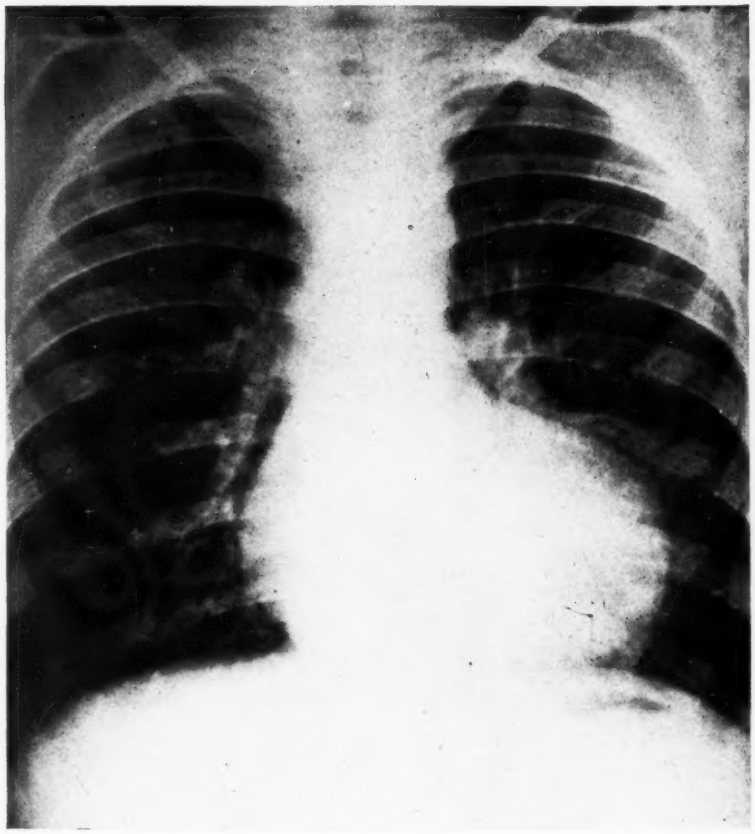


FIG. 14.—Teleradiogram from Case 6, a girl with pulmonary atresia, showing sabot-shaped heart with nodular vascular shadows in the left hilum.

but the vascular shadows extend higher than usual; on the left there are dense nodular shaped vessels at the hilum; on both sides the attenuation of the vascular markings towards the periphery of the lung fields is easily seen.

Angiocardiograms in the antero-posterior position show the aorta and great vessels filled at two seconds and the small pulmonary artery and its left branch indistinctly outlined (Fig. 15). In the left lateral position (Fig. 16) the film taken at two seconds shows the main pulmonary artery overlying the aorta, and dense ill-defined vascular shadows are seen beneath the arch and partially obscuring the aortic window. In the L.A.O. position the outline of the pulmonary artery is seen at two seconds and in addition the origin of the right branch of the pulmonary artery shows as a dense rounded shadow lying behind the ascending aorta.

Post-mortem, the infundibulum of the right ventricle was minute and ended bluntly in the fused pulmonary valves. The pulmonary trunk was thin walled and its diameter less than one-quarter that of the aorta: the left and right branches were also small and thin walled. Three large bronchial arteries arose from the inferior aspect of the arch of the aorta; one passed to the right and two to the left hilum of the lung. An anomalous artery arising from a coronary sinus opened into the main

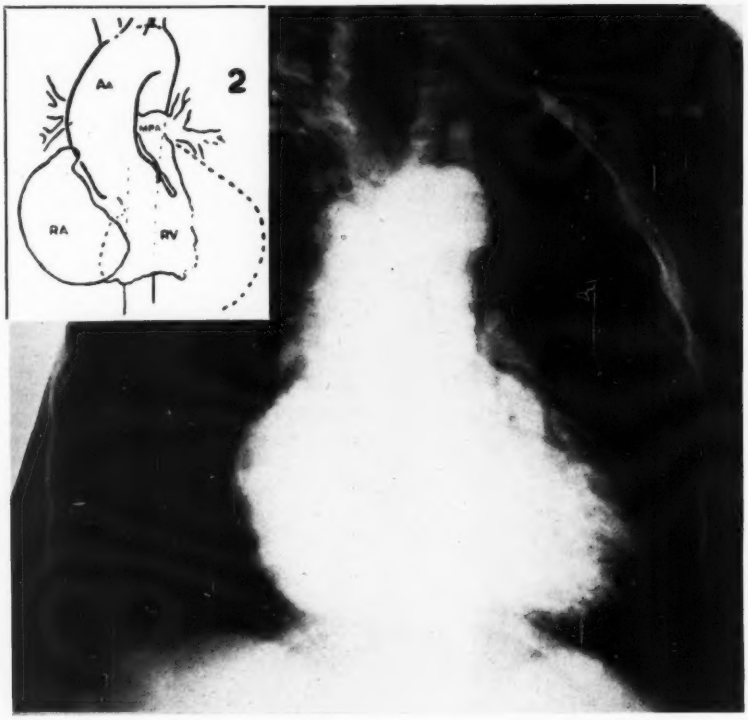


FIG. 15.—Angiocardiogram at 2 sec. in A–P position, from Case 6. Diodone is present in the right auricle and ventricle and the over-riding aorta. The tiny pulmonary trunk (that filled from an anomalous vessel) and its left branch are faintly outlined.

pulmonary trunk immediately distal to the fused pulmonary valves. The ductus arteriosus was closed so it was presumably this anomalous artery that was responsible for the continuous murmur.

DISCUSSION

The radiological appearances of enlarged bronchial arteries and other collateral vessels probably take many bizarre forms. We have attempted to describe those with which we have become familiar and we are confident that these can be recognized in teleradiograms. When the collateral circulation to the lungs is responsible for only a small part of the pulmonary blood flow and is therefore only slightly increased, a hilar comma may be present and recognition of the anomalous vessels may be more difficult. In these circumstances even angiocardiograms may fail to establish their presence with certainty.

Other collateral arteries, as well as the enlarged bronchial arteries, may perhaps be responsible for the abnormal shadows we have described, though post-mortem evidence suggests that the nodular shadows generally represent the latter. The distinction is, however, largely academic and has little bearing on clinical diagnosis or therapeutic procedures.

The significance of continuous murmurs in patients with cyanotic congenital heart disease is of interest. Three of our patients had such continuous murmurs, often best heard at sites that would be unusual for a patent ductus arteriosus. In the first with truncus arteriosus there was no proof of

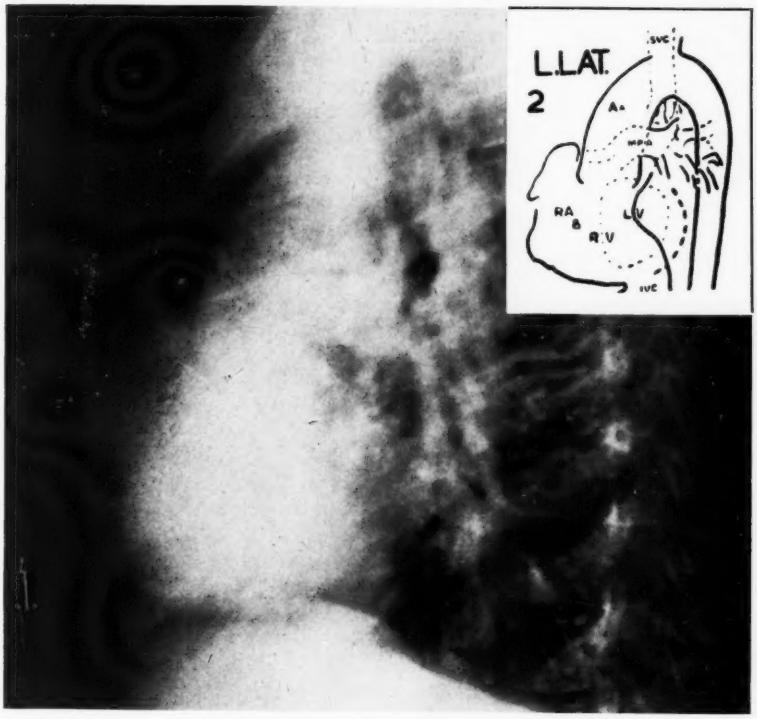


FIG. 16.—Angiocardiogram at 2 sec. in the left lateral position from Case 6. The film shows the pulmonary trunk overlying the aorta, and bronchial arteries in the concavity of the aortic arch. The small vessels in the lung fields that are abnormally straight and narrow are the branches of the bronchial artery.

where it was produced. In the second, there was a large bronchial artery, but again no proof that it was produced here. In Case 6, the continuous murmur heard on the left in front was probably due to the anomalous collateral artery: at operation, however, a continuous thrill was felt in the large bronchial artery, running into the right lung.*

SUMMARY

The radiological appearances of enlarged bronchial and collateral arteries are described in seven patients. In the first, the presence of these arteries rests only on clinical and radiological evidence; in the second, similar evidence is supported by the findings at operation. In the five other patients the teleradiograms showed anomalous pulmonary vascular markings; enlarged bronchial arteries and in some instances other collateral arteries were found post-mortem.

Absence of the hilar comma and a deep rounded pulmonary bay, often unusually sharply marked, suggest an anomalous pulmonary blood supply.

Dense vascular shadows, high in the mediastinum and nodular hilar structures with abnormal

* We have seen 25 cyanotic cases with such continuous murmurs and hope to deal with their causation more fully, but we think they are produced most often in enlarged bronchial or other collateral arteries in cases of truncus arteriosus or pulmonary atresia. Sometimes, but much less often, they are due to a true patent ductus arteriosus in cases of pulmonary atresia or Fallot's tralogy.

branching in the lung fields are evidence of the presence of collateral circulation and enlarged bronchial arteries. The changes in the mediastinum are best seen below the aortic arch in the left anterior oblique position and high up on the right in the antero-posterior position where they broaden the pedicle of the heart and show dense vascular markings out to the right. On the left, rounded nodular shadows in the pulmonary bay, that may be separated from the cardiac contour, are characteristic of enlarged bronchial arteries.

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PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY

AN AUTUMN MEETING of the British Cardiac Society was held at the Royal Society of Medicine, London, on October 26, 1949.

The Chairman, S. Boyd Campbell, took the Chair at 10 a.m.; 91 members and 32 visitors were present.

SHORT COMMUNICATIONS

TRANSPOSITION OF THE AORTA AND PULMONARY ARTERY

BY MAURICE CAMPBELL AND S. SUZMAN

Most cyanotic children with congenital heart disease have light lung fields on screening, and some hollowing of the pulmonary bay, showing a diminution in the amount of blood reaching the lungs. Some, however, show the lung shadows much increased round the hilum and for varying distances out into the lung fields. Sometimes in these cases the right and left pulmonary arteries are greatly enlarged, with striking pulsation there and even in the smaller branches out to the periphery, though the degree of prominence of the pulmonary arc is variable.

The picture is like that of auricular septal defect in acyanotic cases, and at first, we looked on these patients as having this septal defect in addition to some other factor causing their cyanosis. After conversations with Helen Taussig in 1948 we thought that this extra factor was transposition of the aorta and pulmonary artery and that the septal defect was more often ventricular, though we have little post-mortem evidence in support. This is very different from Taussig's picture of transposition in infancy with its gloomy prognosis; if, however, the defects in the septa are such that more adequate mixing of the circulation of the two sides of the heart is possible so that the infant survives, there is no reason why it should not continue to do so.

Of children attending a clinic that is mainly composed of cyanotic heart disease, about 6 per cent belong with certainty to this group with increased lung shadows, that we have called *pleonæmic*. We think many of those with moderate or severe cyanosis have transposition of the aorta and pulmonary artery.

We have not subjected many of these children to special investigations, as at present they cannot be helped like cases of Fallot's tetralogy. In three patients, however, cardiac catheterization has shown that the oxygen saturation of the pulmonary artery was considerably higher than of the systemic arteries and aorta, proving that functionally at least, there was transposition. In one, angiocardiography added good supporting evidence and proved that the aorta arose from the right ventricle in the normal position of the pulmonary artery and suggested that the pulmonary artery arose from the left ventricle, though possibly slightly over-riding the right. In the other two, the aorta certainly connected with the right ventricle but seemed more anterior and more in the position found in Fallot's tetralogy, and again there was evidence of the pulmonary artery arising from the left ventricle.

We have selected 30 consecutive cases, that we thought pleonæmic, from about 400 patients with cyanotic congenital heart disease. The selection has been entirely on the appearance of the lung fields on radioscopy and the teleradiograms; and expansile pulsation of the pulmonary branches has been the most decisive criterion, though a few cases have been included on the general appearance without the certainty of expansile pulsation.

We thought 23 of these children had complete or partial transposition of the aorta and pulmonary artery and that 7 of the older patients, who will not be referred to further, had Eisenmenger's complex.

In these cases of transposition, the cyanosis is as severe as in Fallot's tetralogy and has even more tendency to be noticed from birth. Perhaps the hæmoglobin is not so often above 140 per cent, but the appearance and clubbing of the fingers may be just the same. Only a few of these children squatted habitually.

The systolic murmur is generally maximal on the left rather below the pulmonary area, but is variable and is absent in a third. A thrill may accompany this, much less often than with Fallot's tetralogy. About a quarter of those children have a diastolic murmur, generally maximal in the pulmonary area.

The most important physical sign is the loudness of the pulmonary second sound, which may be palpable; it suggests that a large pulmonary artery will be seen on screening, probably with high pulmonary pressure. This alone may be enough to exclude Fallot's tetralogy.

Sometimes the pulsation seen on screening amounts to a well-marked hilar dance and we hoped we might get a good correlation between this and the presence of the diastolic murmur, indicating that it was due to pulmonary regurgitation, but the correlation is not close. The heart is larger and of a different shape, generally with some prominence in the pulmonary region. The general mottled density of the lungs is often obvious on the film, but is better judged on screening where there seem to be two types, those with great dilatation of the main branches of the pulmonary artery, and those with more general mottling.

The right ventricle is enlarged more than the left on radioscopy, though perhaps there is not as much difference as with Fallot's tetralogy. Right ventricular preponderance is as common electrocardiographically and it is not easy to distinguish between this group and Fallot's tetralogy as both also show a large pointed P wave in lead II.

Difficulty in diagnosis may arise when there is a heavy collateral circulation to the lungs. As a general rule this shows an increase of linear markings in the lung fields, or small rounded spots when the vessels are seen in section, as opposed to the denser and larger patchy shadows, often with clearly defined edges; these, if large enough, may show expansile pulsation or changing density on radioscopy, and this is really pathognomonic of increased pulmonary circulation or to a lesser extent of increased pulmonary pressure.

Lesser Known Features of Ventricular Septal Defect

By Paul Wood

It is generally understood that ventricular septal defect (V.S.D.) is the most benign form of congenital heart disease and causes little change of cardiac structure or function, and no abnormal signs except an impressive left parasternal systolic thrill and murmur; its sole past importance has depended on its predisposition to develop bacterial endocarditis. The object of this communication is to stress the rarity of the maladie de Roger, as so described, and to offer evidence suggesting that V.S.D. usually presents a very different picture.

During the last two years at the Institute of Cardiology more than 100 cardiac catheterizations have been carried out on cases of congenital heart disease of all types. There was little manifest selection, nearly all cases of congenital heart disease seen by the speaker being catheterized, and cases of all kinds being referred for diagnosis with no special emphasis on the cyanotic group or on those thought to be amenable to surgical repair.

Amongst the first 100 cases there were eight instances of isolated V.S.D., three of pulmonary valvular stenosis associated with V.S.D., and three with a loud left parasternal systolic murmur proved to have normal hearts. Cyanotic forms of congenital heart disease, with V.S.D. as part of the anomaly, were excluded from this study.

Of the eight with isolated V.S.D. only two were so diagnosed clinically by the physician who first examined them. Erroneous diagnoses were pulmonary stenosis with dilated pulmonary artery, patent ductus without a machinery murmur, mitral stenosis and atrial septal defect.

The clinical features included a small peripheral pulse, tumultuous cardiac impulse representing a greatly increased stroke volume of the left ventricle, a functional mitral diastolic murmur due to turbulence at the mitral orifice caused by the torrential mitral blood flow, a loud systolic murmur with or without a thrill over the dilated pulmonary artery, accentuation and splitting of the second heart sound, and occasionally pulmonary incompetence. Although a systolic thrill and murmur were noted as low as the fourth left intercostal space close to the sternum in six of the eight cases, it was usually insufficiently localized to determine the diagnosis.

X-rays commonly showed conspicuous dilatation of the pulmonary artery and its main branches, gross exaggeration of the pulmonary vascular shadows, hypoplasia of the aortic knuckle, considerable enlargement of the left ventricle, and slight dilatation of the left auricle.

The electrocardiogram showed partial right bundle branch block in six of the eight cases.

Catheter studies revealed considerable elevation of the right ventricular and pulmonary artery pressures in the majority, the actual mean pressure in the right ventricle in cm. of saline above the sternal angle being 15, 25, 39, 65, 59, 18, 30, and 32; and the pulmonary artery pressures being 18, 25, ?, 130, 100, 24, ?, and 57 respectively. Samples from the superior vena cava and right auricle showed ordinary venous blood about 70 per cent saturated; samples from the right ventricle, whether from low, mid or high positions, were conspicuously arterialized and were commonly 80–85 per cent saturated, pulmonary artery samples being similar. Samples from the femoral artery were 92–95 per cent saturated, none of the cases being cyanotic, by definition.

It is concluded that the left parasternal murmur, which gave rise to the belief that ventricular septal defect was the commonest form of congenital heart disease seen at school age, is in fact innocent; that the maladie de Roger as classically described is rare; and that ventricular septal defect usually results in the changes outlined above.

Since the facts have been known, considerable difficulty has been experienced in distinguishing clinically between ventricular and atrial septal defects. (Patent ductus without a machinery murmur is excluded by the peripheral circulation.) A small pulse, hypoplasia of the aorta, clinical and radiological evidence of pulmonary plethora, a mitral diastolic murmur, splitting of the second heart sound, and right bundle branch block occur in both. If the cardiac impulse is tapping, A.S.D. is probable; if tumultuous, V.S.D. is favoured, but not with much assurance. A relatively low systolic thrill and murmur to the left of the sternum favour V.S.D. If enlargement of the left ventricle can be demonstrated radiologically in the second oblique position, V.S.D. is probable. Finally, the right bundle branch block pattern in V.S.D. usually shows a conspicuous S wave in lead V1, indicating enlargement of the left ventricle; in A.S.D. the S wave is small.

Atrial Septal Defect with Special Reference to the Electrocardiogram

By J. M. Barber and O. Magidson (*introduced by* Paul Wood)

Until very recently the diagnosis of atrial septal defect (A.S.D.) has been based almost entirely on the radiological appearances; but it has become increasingly obvious, since the introduction of cardiac catheterization, that these X-ray signs may be far less conspicuous than those originally described, and that certain clinical features supported by a characteristic electrocardiogram are equally if not more reliable.

During the past two years at the Institute of Cardiology we have studied 60 cases of atrial septal defect, 15 of which were confirmed by means of cardiac catheterization. Special care was taken to exclude pulmonary heart disease, mitral stenosis, ventricular septal defect, patent ductus arteriosus and such uncommon conditions as primary pulmonary hypertension and idiopathic dilatation of the pulmonary artery; if there was any doubt, cardiac catheterization was performed.

There were 41 females to 15 males in this series, and the ages ranged from 6½ to 66 years, more

than half being over 30 years of age. Dyspnœa on exertion was the only common symptom. Persistent cyanosis was seen in only three patients, and each of these had heart failure. In all cases the pulse was of small volume. In the majority, the apex beat was displaced to the left and had a characteristically tumultuous quality associated with an overfilled right ventricle. A systolic thrill at the pulmonary area was felt in nearly one-third, and a systolic murmur was heard in all. The Graham Steell murmur of functional pulmonary incompetence was present in two-thirds, and was common to all age groups. Noticeable grade III splitting of the second heart sound was present in most cases, and a third heart sound was heard in about 30 per cent. Eight patients had a mitral diastolic murmur, and seven had congestive heart failure.

The electrocardiographic findings are shown in the accompanying table. The electrical axis was usually normal or deviated to the right, but left axis deviation occurred in seven. A slightly prominent P wave was seen in 22 cases, but a well defined " P pulmonale " was rare. This correlates well with the relatively low mean right ventricular pressures found on cardiac catheterization. The P–R interval was a little prolonged in 35 cases. There were seven instances of auricular fibrillation and one of auricular flutter.

The ventricular complexes were of great interest and showed the pattern of partial or complete right bundle branch block in 57 of the 60 cases (95%). The remaining 3 cases showed right ventricular dominance. Right bundle branch block was often by no means obvious in standard leads; the diagnosis depended largely upon the presence of an RSR complex in lead V1 associated with a slurred S wave in leads V5 and V6.

The pattern of right bundle branch block may be attributed to the overfilled right ventricle, a condition necessarily present from birth. While it is in no way specific to A.S.D., its relative rarity in other right-sided lesions is stressed. Thus we found but four such tracings in 64 unselected cases of mitral stenosis, three in 33 cases of Fallot's tetralogy, four in 100 cases of chronic pulmonary heart disease, and three in 11 instances of pulmonary stenosis.

It is concluded that partial or complete right bundle branch block is not only an extremely important positive sign of atrial septal defect, but that such a diagnosis may be virtually excluded in its absence.

ELECTROCARDIOGRAPHIC DATA IN 60 CASES OF ATRIAL SEPTAL DEFECT

Electrical Axis	
Normal	17
Right axis deviation	36
Left axis deviation	7
P Wave	
Height greater than 2·5 mm. in lead II	2
2·0 to 2·49 mm. in lead II	22*
Width of P in lead II greater than 0·11 seconds	11
P–R Interval	
0·20 to 0·22 seconds	24
0·23 to 0·25 seconds	5
0·26 and greater (4 cases 0·26, 2 cases 0·28)	6
Right Bundle Branch Block	
0·12 seconds or greater	23
0·09 to 0·11 seconds	34
Right Ventricular Hypertrophy pattern without Right Bundle Branch Block	3
Height of R^1 in Lead V1 in Right Bundle Branch Block Cases	
Over 15 mm.	3
10 to 14·9 mm.	5
5 to 9·9 mm.	32
Auricular Fibrillation	
(Patients aged – 43, 48, 49, 50, 51, 59, 62 years)	7*
Auricular Flutter	
(Age of patient 63 years)	1
Normal Sinus Rhythm	52

* 4 with mitral stenosis.

Present-day Trends in the Care of the Cardiac Patient during Pregnancy

By Rae Gilchrist

The main findings from an analysis of 20 years' experience in a Cardiac Clinic attached to the Ante-Natal Department of the Maternity Wing of the Royal Infirmary are presented.

The maternal death rate from rheumatic heart disease is falling steadily but there is still room for improvement. Obstetrical practice and the results obtained vary greatly in different teaching centres. The immediate prognosis for the mother is best gauged according to her myocardial capacity, her age, and her previous obstetrical experience. A statistical analysis shows the importance of these factors.

Maternal deaths can be prevented by improved selection of patients in the early days of pregnancy and by the avoidance of obstetrical interference in the later months. The main trends in present-day care of the cardiac patient in pregnancy are the enforcement of more prolonged periods of rest throughout the pregnancy and the avoidance of Cæsarean section. Even in grave cardiac distress statistical evidence suggests that pelvic delivery is safer than abdominal, and with other means available sterilisation cannot now be held to justify Cæsarean section amongst women with heart disease.

Uræmia Complicating Low Sodium Treatment of Heart Failure

By A. B. Black and J. A. Litchfield (*introduced by* O. Brenner)

Eight cases are described in which uræmia developed during treatment of heart failure by a combination of restriction of sodium intake and mercurial diuresis. Evidence is presented to show that this was the result of salt depletion rather than of renal structural damage. The effect of salt depletion on renal function is briefly discussed and treatment is suggested to combat this complication.

Low Sodium Diet : Effect on Weight of Added Sodium

By D. R. Cameron

A number of patients with congestive heart failure who had lost œdema on routine digitalis and diuretic treatment in conjunction with the low sodium diet, were observed until their weights became stable. On the same regime, except for the addition of 2 g. sodium chloride daily, it was found that a significant weight increase occurred almost invariably. A similar weight increase occurred with the addition of 2 g. sodium bromide daily, but no significant increase occurred with lithium chloride.

A small control group of patients suffering from Ménière's disease, likewise given a diet low in sodium, did not show a similar weight increase when sodium chloride was added to their low sodium diet.

These variations in weight appeared to be associated with variations in urinary sodium excretion.

A Reassessment of the Effort Test in Angina Pectoris

By M. McGregor, O. Magidson, W. Whitaker (*introduced*) and P. Wood

At least one-third of patients with angina pectoris, who give no history of cardiac infarction, have normal electrocardiograms at rest; when such patients are subjected to effort, the electrocardiogram may show significant depression of the S–T segment. There has been little agreement about the value of this test, and reported results have shown wide variation; positive curves have rarely exceeded 50 per cent. The Levy anoxia test has proved little better.

It has been the common practice to standardize the effort given according to age, sex, and weight, in the belief that the changes found in normal controls and ischæmic cases differ only in degree. In our opinion this is incorrect; there are certain changes never seen in controls that we believe are pathognomonic of myocardial ischæmia.

In this investigation cases were divided into two groups:

(i) 63 cases of typical angina pectoris with normal electrocardiograms at rest;
(ii) 87 cases made up of 50 normal subjects aged 20–68, and 37 patients with clinically innocent chest pain.

Procedure. Standard, unipolar limb, and multiple V chest leads were recorded at rest; with the electrodes still strapped on the limbs, the patient was then exercised to the limit of his capacity. Most frequently we used a small step 12 inches high upon which the patient climbed up and down as rapidly as possible. On the whole the controls performed two to four times as much work as those with angina, because their effort tolerance was less limited. The majority of patients with angina developed pain, but by no means all. Immediately the patient stopped the electrocardiogram was repeated. A direct writing instrument was favoured so that the most informative lead, usually V5, could be recognized at once. Records were then obtained from this lead at half-minute intervals until the graph returned to normal.

Assessment of results. Positive curves showed any of the following changes in left ventricular surface leads or their equivalents:

(1) Complete flattening of the T wave.
(2) A bisphasic T wave, the first part being negative.
(3) Inversion of the T wave.
(4) Flat depression of the S–T segment of at least 1 mm.

Depression of the S–T origin alone, followed by a sharp upwardly sloping S–T segment was common in controls.

Inversion of the U wave occurred in four cases, and partial left bundle branch block in one.

Results. In the controls there was one strongly positive and two doubtfully positive curves. Of the 63 ischæmic cases, 82 per cent yielded positive curves. Most of those with negative curves did not perform much work, and this was reflected in the lack of cardiac acceleration. Of those who developed a heart rate of 90 beats a minute or more, 90 per cent were positive. Greater weight should be attached, therefore, to a negative result when associated with tachycardia.

An Evaluation of the Anoxæmia Test for Coronary Insufficiency

By R. W. D. Turner

Physicians have long felt the need for some confirmatory test when coronary insufficiency is suspected but cannot be proven; that is to say when physical examination and resting electrocardiograms are normal. Assistance would be particularly welcome when the history is not quite characteristic. Preferably too a negative result would exclude angina as the basis for an atypical pain. An objective test is better than a clinical impression. To this end a number of procedures have been devised and include adrenaline, pitressin, and anoxæmic and exercise tests. The latter is the most familiar and most closely reproduces the circumstances under which pain is naturally experienced but carries the disadvantages that electrocardiograms cannot be recorded until after the exertion is over, while not all patients can take sufficient exercise; moreover, though the exercise can be stopped should pain or any untoward symptoms ensue its effects may not be rapidly reversible. The anoxæmic test offers certain advantages. A mixture containing 10 per cent oxygen and 90 per

cent nitrogen is administered through an anæsthetic mask. The patient is resting and, if confidence has been gained, relaxed. Records are easily made throughout the test and should any untoward symptoms occur 100 per cent oxygen is always immediately to hand. Details of the technique are described and the criteria of abnormality analysed. Fifty patients including 20 controls have been studied as opportunity offered over the past two years. Reactions have been few, not serious, and related to cerebral rather than myocardial anoxia.

This review was undertaken because of doubts concerning some of the published claims. The dividing line between changes in normal controls and patients cannot be drawn exactly. A negative test does not exclude coronary disease. However, information of some value was obtained in 50 per cent of the patients. It is concluded that the test is safe but plays no more than a small role in the assessment of difficult cases.

A Personal Follow-up in 111 Cases of Intra-ventricular Heart Block

By Henry Moore

Criteria of the New York Heart Association (1946) were followed with the three standard limb leads and lead IV F. Amongst 3000 patients electrocardiographed 111 (or 4%) showed intra-ventricular heart block (I.V.B.), whereas there were only 13 cases of A–V block. In an analysis of the 111 cases of I.V.B., men were exactly twice the number of women; the heaviest incidence was between 50 and 70 years of age, but many occurred between 40 and 80; the longest survival rates in 88 patients who had died were 19 years in left branch block, 5 years in right branch block, and 10 years in indeterminate forms. Among the 111 cases there were 70 per cent of left branch block, 7 per cent of right branch block, and 23 per cent of indeterminate forms. Bundle branch block was clinically correctly suspected in 64 per cent. The average duration of life to the nearest month from the time of the original diagnosis was as follows: right branch block, 25 months; left, 26 months; and indeterminate forms, 33 months. The chief ætiological factors were vascular hypertension alone in 43 per cent, coronary artery disease alone in 15 per cent, and both together in 6 per cent—these three headings accounting for over 64 per cent of the cases. It is highly likely, however, that the importance of coronary artery disease is very considerably under estimated as several of the hearts showed gross coronary artery disease post-mortem, with no evidence of it during life. Four cases of left bundle branch block and one of right changed to indeterminate forms during observation and in one of them an old lesion was found blocking the left branch and a recent one blocking the right. Six cases showed at least temporary and two permanent disappearance of the bundle branch block (two indeterminate and six left). In four cases I.V.B. was associated with A–V block. In eleven cases the branch block seemed to cause no disability, and in another eleven the survival rate was five or more years (maximum 19 years). In itself I.V.B. is not incompatible with several years of life and with a reasonable degree of physical activity (22 cases in this series). The prognosis seems to depend, not so much on the block itself, but rather (1) on the conditions that caused the block, (2) on the degree of disability or strain to which the heart is subjected by the ætiological factors, and (3) on the ability of the myocardium to " stand up " to these factors. Detailed studies were made of five of these hearts by Professor Keenan with complete tracing of the conducting system. (This work was done under a technical grant from the Medical Research Council of Ireland).

Congenital Absence of the Right Branch of the Bundle of His

By J. B. Coakley (*introduced by* Henry Moore)

In May 1948 a boy, aged 19 years, was admitted to the Mater Misericordiæ Hospital, Dublin, by Professor Henry Moore. His relevant previous history was, that he was " inclined to be blueish " and he complained of " lack of energy." Clinical examination revealed a considerably enlarged

heart with a mitral systolic murmur and a split first mitral sound; his pulse was 84 at rest, and his B.P. was 104/90; there were crepitations at both lung bases and a simple exercise test produced dyspnœa. X-ray examination revealed a markedly enlarged heart, involving especially the right atrium, with a scarcely discernible aortic notch. The electrocardiogram was of an indeterminate form of intraventricular heart block, with possibly lesions in both branches.

On post-mortem examination the heart was enlarged and hypertrophied; the cavity of the right atrium was larger while that of the right ventricle was smaller than normal. The aorta showed hypoplasia, its diameter being 16·5 mm.

The conducting system was investigated by serial section of blocks of tissue embedded in paraffin. The sections were stained with a modification of Masson's trichrome stain, using light green.

The right and left coronary arteries and specially the anterior descending branch of the left coronary showed considerable evidence of atherosclerosis.

Both sinu-atrial and atrio-ventricular nodes were normal. The bundle of His was traced across the atrio-ventricular ring but did not divide into right and left branches as should normally occur. Instead the entire bundle passed into the left branch. This branch was traced carefully. It gave fibres to the muscle of the interventricular septum on the left side and became condensed into four main divisions. These also gave fibres to the muscle of the septum and then the continuity in all four left divisions was completely interrupted by fibrous lesions.

No right branch was present in this heart. The possibility of a lesion in the branch at the bifurcation of the bundle was investigated and excluded. Likewise the possibility of a right branch crossing the atrio-ventricular ring independently of the bundle of His was excluded. No bundle of Kent was present in this heart.

It was concluded, therefore, that the absence of the right branch in this heart must be due to a congenital defect. An attempt was made to explain this deficiency on the basis of the embryology of the heart. As far as we know, no such case has ever been recorded previously.

This work was done under a grant from the Medical Research Council of Ireland.

The Use of Anti-coagulants in Coronary Thrombosis: An Analysis of 170 Cases

By John Tulloch (*introduced*) and Rae Gilchrist

Coronary thrombosis occurring in 170 instances in 164 patients has been closely studied and personally observed. This group constitutes two series of patients (*a*) a control group of 100 cases treated by conventional methods, and (*b*) 70 cases receiving in addition anti-coagulant therapy.

Anti-coagulants were administered during the first three weeks after the onset of infarction. Heparin was employed for the first 4–5 days, by which time dicoumarol became effective. The dicoumarol dosage was regulated by daily prothrombin estimations.

The course followed by the control group has been analysed and the various features of importance in assessing the prognosis are stressed. The treated group has been similarly analysed and the improved prognosis noted.

The Influence of Heart Rate Control on Cardiac Output in Heart Failure

By R. I. S. Bayliss and H. G. Kelly (*introduced by* J. McMichael)

Published in full, Lancet, 1949, 2, 1071.

ABSTRACTS OF CARDIOLOGY

Pure Congenital Pulmonary Stenosis and Idiopathic Congenital Dilatation of the Pulmonary Artery. D. G. GREENE, E. DE F. BALDWIN, J. S. BALDWIN, A. HIMMELSTEIN, C. E. ROH, and A. COURNAND. *Amer. J. Med.*, **6**, 24–40, Jan., 1949.

These conditions are so termed because of the absence of associated septal defects, which rules out abnormal communications between the greater and lesser circulation.

First, the authors review cases published in the last 30 years in which diagnosis has been verified at necropsy: 68 of pure pulmonary stenosis, and 8 of pulmonary dilatation—including 8 personal cases, 4 of pure congenital pulmonary stenosis and 4 of pure dilatation of the pulmonary artery. Dilatation of the pulmonary artery is present in both conditions, verified post-mortem; the differential diagnosis cannot, therefore, be made radiographically, as the cardiac silhouette is similar in both. The presence or absence of murmurs or thrills is of no more value. The determination of the pressure in the right ventricle and the intensity of the second pulmonary sound are important. In pure pulmonary stenosis the pulmonary second sound is either normal or absent; it is always accentuated, and sometimes louder than the aortic second sound, in dilatation of the pulmonary artery. Of the two abnormalities, idiopathic congenital dilatation of the pulmonary artery is much the rarer. *A. I. Suchett-Kaye*

Cardiodynamics of Experimental Interventricular Communications. W. H. DILLON and H. SCHREIBER. *Amer. J. Physiol.*, **154**, 281–289, Aug., 1948.

Experiments on dogs were carried out to study the effects of interventricular communications on the ventricles and to clarify some problems in connexion with interventricular septal defects in human beings. The method used was the creation of an external interventricular shunt which could be either opened or closed to suit experimental conditions. On opening the shunt there was in the left ventricle an elevation of initial pressure, a decline in maximum pressure, and an increase in duration of contraction in relation to cycle length. The predominant changes in the right ventricle consisted in an elevation of both initial and maximum pressures. A further analysis of data suggested that the elevation of right ventricular pressure was not caused wholly by summation of right and transmitted left ventricular pressures, but was partly due to a compensatory response of the right myocardium, which dilated sufficiently to increase the initial length of its fibres.

In left-to-right ventricular shunt the more vigorous right ventricular action had two effects: (1) ejection of a larger volume of blood for return to the left heart: and (2) reduction of the fraction of blood shunted into the right ventricle during systole. In these experiments the aortic pulse pressure invariably fell on opening the shunt, and this was found to be due to a reduced left ventricular stroke volume. This work has also shown that a slow intravenous infusion of saline could restore the aortic pulse pressure so long as the right heart was not failing. *A. I. Suchett-Kaye*

Serial Electrocardiographic Changes in Young Adults with Acute Rheumatic Fever; Report of 62 Cases. N. S. BLACKMAN and C. I. HAMILTON. *Ann. intern. Med.*, **29**, 416–431, Sept., 1948.

In 62 soldiers, aged 17 to 21, admitted to hospital for acute rheumatic fever, serial electrocardiograms were taken every other day during the first week and twice a week thereafter until the patient's discharge for convalescence. The limb leads and lead CF_4 were taken, and lead III was taken during normal respiration and again during held inspiration. Changes were determined by the limb leads alone. Only one case showed entirely normal records throughout. The most important changes were: alterations in T waves and S–T segments in 38 cases; first-degree auriculo-ventricular block in 26; prolongation of the Q–T interval in 22; elevation or depression of S–T segments in 14; other changes in 21 cases. *A. Schott*

Severity and Duration of Hypertension in Relation to Amount of Cardiac Hypertrophy. B. R. STEIN and A. R. BARNES. *Amer. J. med. Sci.*, **216**, 661–664, Dec., 1948.

At the Mayo Clinic in the 6 years beginning Jan. 1, 1940, 111 patients with hypertension, in whom records of normal blood pressure had formerly been obtained, came to necropsy. From the records the duration of hypertension and its [sometimes changing] degree were estimated, preferably from ophthalmoscopic findings but otherwise by manometric readings (Group 1, 140/90 to 200/100 mm. Hg; Group 2, 200/100 to 240/120 mm.; Group 3, above 240/120 mm.; Group 4 was diagnosed only after ophthalmoscopy. Cardiac hypertrophy was expressed in terms of percentage excess of heart weight above the calculated normal referred to body weight, 20% being added. This percentage hypertrophy was found to be closely related to the severity of the hypertension, but not at all related to its duration. Also, except in hypertension of Group 4, there appeared to be

no relation between the severity of the hypertension and its duration.

There was a preponderance of males among the cases in which the heart had become greatly enlarged in the shortest time. The hearts were smaller and there was a fairly constant age incidence among the women, and the percentage of males rapidly dwindled as the duration of hypertension increased. The women of the series seemed to have withstood their hypertension better than the men. *W. A. Bourne*

Hypertension in New Zealand. A Survey of 443 Consecutive Deaths in Dunedin Hospital. K. S. ALSTAD and F. H. SMIRK. *N. Z. med. J.*, **47**, 298–308, Aug., 1948.

By hypertension is meant a condition in which the pressure is greater than 160 mm. Hg systolic, and 90 mm. diastolic. It seems that in New Zealand circulatory disease (including cerebral vascular disease) accounts for over 40% of the total deaths, and is the greatest single cause of death. Moreover, although benign hypertension is common in New Zealand and tends to run a mild course, malignant hypertension and advanced glomerulonephritis are rare, as also are rheumatic fever and rheumatic heart disease; these findings differ from those in Britain and the U.S.A. The writers state that together malignant hypertension and advanced glomerulonephritis only account for 2 out of 169 cases of hypertension. From these and other figures they consider it very probable that malignant hypertension is not merely an accelerated form of benign hypertension but is either a separate condition or involves some additional factor.

In the present series, more than half of the deaths from circulatory disease occurred in patients with hypertension, and considerably more frequently in men than in women, although the sex difference as regards actual numbers of hypertensive subjects was not so great. From this it is inferred that the female vascular system tolerates hypertension better than does the male. By far the greatest proportion of deaths (about 55%) in hypertensive subjects occurred between the ages of 60 and 80, although elsewhere it is shown that, from the age of 20 onwards and particularly after 50, high blood pressure plays an increasing part in determining the mode of death. *T. E. C. Early*

Massive Hypertrophy of the Heart with Special Reference to Bernheim's Syndrome. L. R. EVANS and P. D. WHITE. *Amer. J. med. Sci.*, **216**, 485–491, Nov., 1948.

In 1910 and 1915 Bernheim published his view that a hypertrophied left ventricle by partial occlusion of the right ventricular chamber could produce the signs of right ventricular failure in the absence of pulmonary congestion.

The authors have studied the clinical and necropsy records in 33 cases of massive hypertrophy of the heart to at least twice the normal weight. Of these 33, 22 showed left ventricular hypertrophy. Four points were studied: (1) the initial symptoms of heart failure; (2) the weight of the liver and the lungs; (3) hearts with a left ventricular myocardium at least twice as thick as the right; (4) right auricular enlargement in the X-ray films. On the grounds of history alone no case was acceptable as one of Bernheim's syndrome. Comparison of the weights of the liver and lungs failed to suggest any evidence of Bernheim's syndrome, neither was gross eccentric hypertrophy of the left ventricle found to be associated with the symptoms expected. Finally, right auricular dilatation was not seen in the X-ray films.

The authors sum up by saying that they could find no clear-cut evidence of Bernheim's syndrome in their material. *John Anderson*

Laryngeal Paralysis Associated with Cardiac Hypertrophy. Report of Four Cases. F. T. LAND. *Brit. med. J.*, **2**, 1018–1019, Dec. 11, 1948.

Paralysis of the left vocal cord associated with heart disease is relatively infrequent, about 80 cases having been reported. This article deals with 4 cases, in 3 of which there was mitral stenosis. The possible mechanisms producing paralysis are discussed, and it seems most likely that the dilatation of the pulmonary artery leads to compression of the left recurrent laryngeal nerve against the arch of the aorta and the ligamentum arteriosum. Dilatation of the pulmonary artery is a constant feature in mitral stenosis, certain forms of congenital heart disease, and in arteriosclerotic heart disease with failure of the left ventricle. The reported cases mainly fall into these groups. *James W. Brown*

Long Term Anticoagulant Therapy for Cardiovascular Diseases. W. T. FOLEY and I. S. WRIGHT. *Amer. J. med. Sci.*, **217**, 136–142, Feb., 1949.

In this important paper the authors describe the effect of administration of dicoumarol to 19 patients for periods of 5 to 20 months. The patients receiving this treatment were those whose lives would otherwise have been severely restricted and in danger—patients with auricular fibrillation and a history of frequent embolic attacks, with phlebitis migrans and recurrent thrombophlebitis, and also some with coronary thrombosis and cardiac infarction. These patients were kept in hospital for a short period while their idiosyncrasies to the drug were studied, and thereafter reported twice weekly for prothrombin estimation and regulation of their dose of dicoumarol. In very stable cases the period between prothrombin estimations may be extended to 10 or even 14 days but this is not generally advised. Only intelligent patients who can be relied upon to report regularly for prothrombin estimations and to take exactly the prescribed dose of dicoumarol should be selected for this type of therapy.

The Link–Shapiro modification of Quick's method was used for the estimation of prothrombin time, which was kept as far as possible between 30 and 35 seconds, the normal figure being 14 to 16 seconds. The thromboplastin used was checked daily to ensure its activity. Individual requirements of dicoumarol were found to vary between 175 and 800 mg. weekly, and did not seem to be related to age or weight, but to be affected by such things as protein consumption and, in one patient, by

the amount of whisky taken. The prothrombin time was not affected by menstruation in most patients, nor was menstruation prolonged in patients receiving the correct dosage of dicoumarol. Water-soluble vitamin K analogue, 72 mg. 4-hourly, was given intravenously to patients whose prothrombin time exceeded 60 seconds. None of the patients showed any toxic effects, none had a serious hæmorrhage, and all remained free from further thrombo-embolic episodes while under treatment.

G. S. Crockett

Failure of the Heart and Circulation. TERENCE EAST. 2nd ed. London: Staples Press Ltd., 1948 (pp. 144. 8*s.* 6*d.*)

The author has contrived to incorporate in his new edition the results of much of the work on the hæmodynamics of the circulation that has developed during recent years with the use of the intracardiac catheter and other new techniques in cardiology. This has meant an extensive revision of the text, but the result is a successful handbook full of sound explanations and practical advice. He is careful to point out that the interpretations of some of these researches may still have to be revised, but emphasizes that many of the older ideas about heart failure have already been rendered obsolete. This probably explains why he does not commit himself about the value of digitalis in high output failure, yet, in spite of the contrary experimental evidence, many clinicians continue to acknowledge its usefulness. Not all will agree with the author's declared approval of theophyllin-ethylenediamine, nor with the clinical acceptance of Bernheim's syndrome, and mention might advantageously have been made of the routine digitalization of middle-aged patients with thyrotoxicosis before thyroidectomy as a valuable measure in preventing post-operative congestive failure.

J. L. Lovibond

The Use of the Anticoagulants in the Treatment of Diseases of the Heart and Blood Vessels. I. S. WRIGHT. *Ann. intern. Med.*, **30**, 80–91, Jan., 1949.

The number of deaths from coronary thrombosis can be substantially, reduced as also can thrombo-embolic complications in endocarditis and cardiac infarction, by the proper use of anticoagulant therapy. This conclusion is based on the study of 1000 cases collected from 16 major hospitals on the eastern American seaboard. In this report are incorporated 800 case records. There are also a small series of 22 cases of rheumatic heart disease with auricular fibrillation and multiple embolic phenomena, and a further series of 19 patients for whom long-term ambulatory anticoagulant therapy was arranged.

The author believes that hæmorrhage in the course of anticoagulant therapy is an overstressed danger, but he issues a warning that prothrombin estimations must be made by a skilled technician, and that there are certain obvious contraindications, such as visceral organic disease or possible bleeding surfaces.

G. F. Walker

Venous Thrombosis and Anticoagulants. K. P. BALL and H. O. HUGHES. *Brit. med. J.*, **1**, 560–565, April 2, 1949.

The authors describe 100 consecutive patients treated by them with anticoagulants, and review the present status of venous thrombosis with particular reference to incidence, sites of development, clinical features, the chief complication (pulmonary embolism), and the late sequelæ (varicose veins and ulcers). They discuss treatment fully, and analyse its results in their series. They compare heparin and dicoumarol, and state the qualities necessary in an ideal anticoagulant.

Dicoumarol therapy needs strict clinical control and a reliable technique of prothrombin-time estimation. The authors describe such a technique. An appendix gives details of their methods and of commonly encountered difficulties.

A. S. Dixon

Pulmonary Embolism and Infarction in Patients with Cardiac Disease. Their Relation to Venous Thrombosis. J. LENEGRE, A. MATHIVAT, G. CAROUSO, and J. DE BRUX. *Bull. Soc. med. Hop. Paris*, **65**, 219–229, 1949.

At necropsy on 99 patients who died from cardiac disease pulmonary infarcts or organized thromboses of the pulmonary arteries were found in 20, of whom 17 also had venous thrombosis of the lower limbs. Right-sided intracardiac thrombi were found in 8 of these 20 patients; 2 of the 8 had no venous thromboses in the lower limbs. The internal plantar and posterior tibial veins and collaterals were most commonly the site of thrombosis, which was usually recent and unassociated with phlebitis. Inflammatory changes were also rarely present in the pulmonary arteries. In 14 of these cases pulmonary infarction with thrombosis of the corresponding pulmonary artery and venous thrombosis in the lower limbs coexisted. The authors conclude that pulmonary infarction is commoner than has been indicated in previous descriptions of necropsies on patients dying from cardiac disease, and is usually associated with thrombosis of the corresponding pulmonary artery, which in the majority of cases is due to an embolus from a thrombosed internal plantar or posterior tibial vein.

[Observations of right ventricular pressure in 5 of these cases, presumably by means of cardiac catheterization, might well have led to an increased incidence of pulmonary emboli being reported.]

I. Ansell

Treatment of Congestive Heart Failure. H. A. REID and W. HUGHES. *Lancet*, **1**, 593–598, April 9, 1949.

In this study of 107 patients admitted to hospital with congestive heart failure during a period of 6 months particular regard has been paid to fluid and salt balances. In most cases the therapeutic contribution of salt restriction could not be assessed, as improvements which occurred may have been due to concurrent treatment. But in 4 cases, one of which it described, improvement appeared to be a direct result of a change to a regimen of salt restriction. [Even in the published case, however,

the change to a restricted salt intake and the clinica improvement both coincided with an increase in the frequency of mersalyl injections.]

Salt excretion, with or without a water diuresis, increases when mercurial diuretics are given. Œdematous patients who complain of thirst and of dry tongue are "brine-logged" rather than water-logged, and can be clinically relieved by a low-sodium diet and mersalyl injections, even when, as in one case, water intake is also restricted. In the acute stage of congestive failure, forcing fluid intake above 3½ litres daily has proved dangerous. Some patients who have recovered from congestive failure under treatment in hospital may be maintained at home on a salt-restricted diet without digitalis or mercurials. In such cases the value of salt restriction is indicated by the return of œdema when a free salt intake is allowed.

Practical measures for salt restriction in patients in hospital or at home are discussed. *A. S. Dixon*

Syndrome of Short P–R Interval with Abnormal QRS Complexes and Paroxysmal Tachycardia. L. WOLFF and P. D. WHITE. *Arch. intern. Med.*, **82**, 446–467, Nov., 1948.

The syndrome of short P–R interval with abnormal QRS complexes and paroxysmal tachycardia was first described by Wolff, Parkinson, and White in 1930 (*Amer. Heart J.*, **5**, 685). The 11 cases then described have been followed up and 41 new cases added to the series.

It is shown that this syndrome occurs commonly in young people and more often in males than females. Paroxysmal tachycardia was present in addition to the electrocardiographic abnormalities in 70% of the cases. The syndrome is compatible with a full healthy life and strenuous activity and, apart from the occurrence of paroxysmal tachycardia, is asymptomatic. Errors in the interpretation of the electrocardiogram are not uncommon. Usually the sum of the P–R and QRS intervals is the same in the normal and abnormal beats, but this is not always so. The authors consider that the accumulated evidence favours an accessory conducting pathway as the cause of the abnormality. Digitalis may or may not affect the abnormal complexes. In the majority of cases the electrocardiogram in a paroxysm of tachycardia shows normal ventricular complexes.

C. Bruce Perry

Massive Dilatation of the Left Auricle. R. DALEY and R. FRANKS. *Quart. J. Med.*, **18**, 81–92, April, 1949.

Fifteen cases of massive dilatation of the left auricle are described. All the patients had mitral stenosis and incompetence and in all but one the auricles were fibrillating. Owing to the absence of pulmonary hypertension little complaint was made of dyspnœa. One patient was hoarse because of a recurrent laryngeal palsy; another had erosion of the 7th to 9th dorsal vertebræ. Ten complained of deep-seated pain in the right upper part of the chest; this was ascribed to ischæmia of the auricular wall.

Clinical signs due to the massive size of the left auricle were pulsation to the right of the sternum and dullness at the right base. Bronchiectatic changes from partial occlusion of bronchi were common; occasionally areas of segmental collapse were found. Bronchograms showed widening of the bronchial angle. The authors suggest that the condition may be due to the impingement of blood, because of mitral incompetence, on a left auricular wall, which has been weakened by a rheumatic infection. *C. W. C. Bain*

The Coronary Vasodilator Action of Khellin. G. V. ANREP, M. R. KENAWY, and G. S. BARSOUM. *Amer. Heart J.* **37**, 531–542, April 1, 1949.

Khellin is a crystalline substance extracted from the fruit of Ammi Visnaga, an eastern Mediterranean plant known to Arabic medicine as Khella. Decoctions of the seeds have been used as an antispasmodic since ancient times. The authors compared the coronary vasodilator action of khellin with that of aminophyllin, using both the heart-lung preparation and the isolated rabbit heart. Khellin was found to be about four times as effective as aminophyllin. Since it has a prolonged action khellin is useful in the treatment of angina pectoris; it is given orally in doses of 50 to 100 mg. three times a day, or intramuscularly in doses of 100 mg. once or twice daily. The authors have treated 250 patients with angina pectoris with khellin; the results were good in 56% and moderate in 34%. In patients subjected to a standard exercise test the exercise tolerance was found to be increased after taking the drug in every case. Khellin did not appear to be of great value in cases of coronary thrombosis. Side effects of the drug were slight. *H. E. Holling*

Negative Results of Tocopherol Therapy in Cardiovascular Disease. C. K. DONEGAN, A. L. MESSER, E. S. ORGAIN, and J. M. RUFFIN. *Amer. J. med. Sci.*, **217**, 294–299, March, 1949.

Three groups of patients were studied: (*a*) 7 with hypertension but with no radiological evidence of cardiac enlargement; (*b*) 7 with hypertension and cardiac enlargement; (*c*) 7 with angina pectoris. All were given tocopherol by mouth in doses ranging from 150 mg. of mixed tocopherols to 600 mg. of α-tocopherol daily, for a month at a time alternating with placebos for a month. The patients were studied for from 5 to 20 months. It was shown that the blood level of tocopherol can be significantly raised by oral administration. No appreciable subjective or objective benefit was observed.

C. Bruce Perry